Management of Prader-Willi Syndrome

Merlin G. Butler
Phillip D. K. Lee
Barbara Y. Whitman
Editors

Fourth Edition

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La Monstrua vestida
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La Monstrua desnudo
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Beginning in the sixteenth century, members of the royal House of Habsburg developed an interest in collecting exotic items and paintings of unusual people, as exemplified by the Ambras Kunst- und Wunderkammer created by Archduke Ferdinand II of Austria (1529–1595). Some Habsburg rulers also collected living human "curiosities" for the entertainment of their court. In 1680, Eugenia Martínez Vallejo, the 6-year-old daughter of José Martínez Vallejo and Antonia de la Bodega (villa de Bárcena, provincia de Burgos, Spain) was added to the court of Charles II, the last Habsburg king of Spain. Her image was recorded for posterity by the "painter to the Queen," Juan Carreño de Miranda (1614–1685), in two paintings entitled "La Monstrua."

It is said that upon viewing these paintings in the Museo del Prado, Dr. Andrea Prader immediately recognized the features of the syndrome that he had described with Drs. Labhart and Willi in 1956 (see Appendix A). Although we may never know if Eugenia Martínez Vallejo had Prader Willi syndrome, these paintings have since been regarded as among the earliest depictions of the condition.

In 1997, a bronze sculpture of La Monstrua by Spanish artist Amado González Hevia ("Favila") was placed on the Calle Carreño Miranda in Avilés, Asturias, Spain, the birthplace of Juan Carreño de Miranda.

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Part I

Diagnosis, Clinical Aspects and Genetics of Prader-Willi Syndrome

1 Clinical and Genetic Findings with Natural History of Prader-Willi Syndrome

Merlin G. Butler and Travis Thompson

Historical and Genetic Overview

Prader-Willi syndrome (PWS) is a complex genetic condition characterized by a range of mental and physical findings, with obesity being the most significant health problem followed by behavioral concerns. PWS is considered the most common genetically identified cause of life-threatening obesity in humans and affects an estimated 350,000–400,000 people worldwide. The Prader-Willi Syndrome Association (United States) is aware of more than 3500 persons with this syndrome in the United States from an estimated pool of 17,000–22,000 [1]. Prader-Willi syndrome has an estimated prevalence in the range of 1 in 8000 to 1 in 38,000 individuals [2, 3]. Although PWS is thought to be one of the more common disorders seen for genetic services, pediatricians may only encounter a few patients during their lifelong clinical practice. Although present in all races and ethnic groups, it is reported disproportionately more often in Caucasians [4]. Most cases are sporadic, but several families have been reported in the literature with more than one affected member, including twins and multiple siblings. The chance for recurrence is estimated to be less than 1%, but in some families where defective control of differentially expressed genes are present, the risk is much higher. If the father carries an imprinting defect (microdeletion) of the imprinting center on chromosome 15, then the recurrence risk is 50% [5–8].

Prader-Willi syndrome was apparently first documented in an adolescent female by J. Langdon Down in 1887 [9], but it was not clinically described in the medical literature until about 70 years later. This adolescent female had intellectual disability, obesity, short stature, and hypogonadism with the condition referred to as polysarcia. In 1956, Prader, Labhart, and Willi reported nine individuals (five males and four females) between the ages of 5 and 23 years with similar clinical findings [10]. Since the 1970s, the disorder has been referred to as the Prader-Willi syndrome.

In 1981, Ledbetter and others [11] reported an interstitial deletion of the proximal long arm of chromosome 15 at region q11–q13 in the majority of subjects with PWS using high-resolution chromosome analysis (Fig. 1.1). The syndrome became one of the first genetic disorders attributed to a chromosome microdeletion detectable with new high-resolution chromosome or cytoge-

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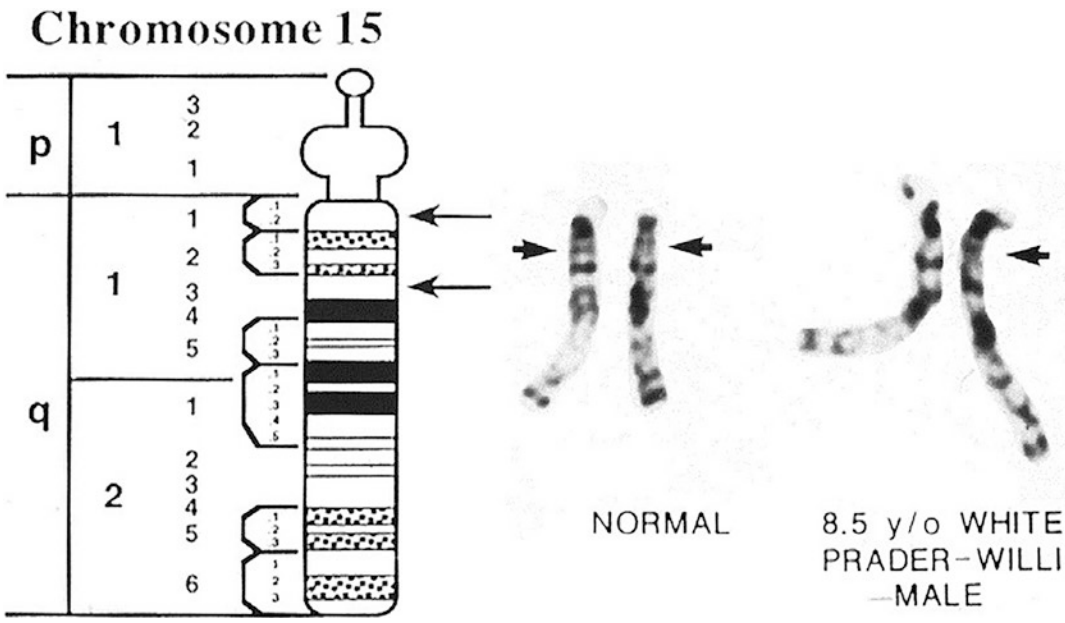

Fig. 1.1 A prometaphase or high-resolution chromosome analysis at greater than 550 band level was first developed in the early 1980s and used to identify small cytogenetic deletions not detectable with routine chromosome banding methods represented by a chromosome 15 ideogram (left). The pattern for chromosome arms (p for short arm and q for long arm) and designated bands are shown with two representative chromosome 15 pairs (right). The arrows on the ideogram indicate the deletion breakpoints at bands 15q11 and 15q13. The 15q12 band is indicated by the arrow on each member of the chromosome 15 pair that is normal. The left member of the chromosome 15 pair from an 8.5-year-old male with Prader-Willi syndrome shows the deletion. (Modified from Butler et al. [13])

netic methods. Later, Butler and Palmer in 1983 [12] were the first to report the chromosome 15 deletion as de novo or a new event. The deletion was not found in either parent but always donated by the father. The parent of origin was determined by studying minor variations or polymorphisms in chromosome structure using different staining methods. This observation was later clarified by using new molecular genetic techniques in the late 1980s. The reporting of a maternal deletion of the same chromosome 15 region was later found in a separate clinical condition recognized as Angelman syndrome (AS).

The cytogenetic deletion of the chromosome 15q11–q13 region was seen in approximately two-thirds of persons with PWS, while the remaining subjects had normal appearing chromosome 15s, translocations, or other chromosome 15 abnormalities [2, 13, 14]. Butler and others in 1986 [13] reported clinical differences in those with PWS with and without the chromosome 15 deletion, particularly a more homogeneous clinical presentation and hypopigmentation in those with the paternal 15q11–q13 deletion. Hypopigmentation and other eye findings (e.g., strabismus), abnormal visual evoked potentials in PWS, were similar to what was found in individuals with classic albinism [15]. Now, high-resolution microarrays, genotyping of chromosome 15 markers, and methylation-specific multiplex ligation probe amplification (MS-MLPA) can be used to describe and characterize the molecular classes seen in PWS.

There are two recognized types of typical chromosome 15q11–q13 deletions, including the larger 15q11–q13 Type I deletion (about 6 Mb in size) involving a proximal breakpoint (BP1) and the typical Type II deletion which is 500 kb smaller in size involving a separate proximal 15q11.2 breakpoint (BP2). The 15q11.2 BP1-BP2 region includes four non-imprinted protein-coding genes (*NIPA1*, *NIPA2*, *CYFIP1*, TUB*GCP5*) involved in brain development and intact in those with the 15q11–q13 Type II dele-

tion but missing in Type I deletion. The 15q11.2 BP1-BP2 deletion (Burnside-Butler) syndrome is an emerging disorder with supporting evidence based on high-resolution microarray testing of patients presenting with developmental delay with or without autism [16]. Hence, these four genes are associated with neurodevelopmental-autism phenotypes when deleted [17]. Individuals with the larger Type I deletion are more affected with compulsions and self-injury with these four genes deleted [18]. Atypical larger or smaller deletions occur in 7–9% of those with PWS and deletions. In a summary, among the 510 individuals with genetically confirmed PWS, 303 (60%) had the paternal 15q11–q13 deletion, 185 (36%) with maternal disomy 15 or both 15s from the mother, and the remaining patients had imprinting center defects or chromosome 15 anomalies such as translocations [19].

Historically, Southern hybridization of polymorphic DNA markers isolated from the 15q11–q13 chromosome region were studied by Nicholls, Butler, and others in 1989 [20] in PWS individuals with normal-appearing chromosomes or non-deletion status. Surprisingly they found that both chromosome 15s were from the mother and none from the father and referred to as maternal uniparental disomy 15 (i.e., both 15s from the mother) or UPD15 (Fig. 1.2). This resulted from an error in egg production due to nondisjunction in female meiosis, most often in the first (reduction) stage of meiosis causing two separate chromosome 15s from the mother. Occasionally, during the second (equational) stage of meiosis, nondisjunction occurs, whereby two identical chromosome 15s from the mother are found in the egg. Due to normal crossover events that may or may not occur in meiosis I, two maternal disomy 15 subclasses are found in PWS, i.e., maternal heterodisomy 15 when no crossover events occur or segmental isodisomy 15 when one or more crossover events occur on the long arm of chromosome 15 leading to segments or regions in which there is loss of genetic polymorphisms with identical DNA signals referred to as loss of heterozygosity (LOH) defined as ≥8 Mb in length [19]. The third form of maternal disomy 15 is total isodisomy 15 found in less than 10% of those with PWS and when UPD15 is present with both chromosome 15s having identical DNA patterns using high-resolution single nucleotide polymorphism SNP microarrays or with complete LOH due to errors in nondisjunction in

Fig. 1.2 Early studies in the 1990s used polymerase chain reaction (PCR) amplification of known genomic DNA markers (e.g., D15S822) from the 15q11–q13 region from a Prader-Willi syndrome family with normal chromosome studies in the Prader-Willi syndrome child. The DNA signals in the mother (on the left), the Prader-Willi syndrome child (in the middle), and the father (on the right) each show two separate DNA bands representing the presence of the D15S822 locus in each chromosome 15 (nondeleted status). The DNA pattern from the mother and Prader-Willi syndrome child are identical, but no DNA signal from chromosome 15 was inherited from the father. The Prader-Willi syndrome child has two chromosome 15s from the mother and no chromosome 15 from the father, demonstrating maternal disomy 15 or both 15s from the mother

meiosis II. When a single chromosome 15 is received from the father in the normal sperm, then trisomy 15 results with three 15s in the fertilized egg. Subsequently, loss of the father's chromosome 15 occurs in early pregnancy through a trisomy rescue event. This loss of a single chromosome 15 in the cells rescues the fetus to avoid a spontaneous miscarriage [21]. Chromosome abnormalities, specifically trisomy 15 and other trisomies and monosomies, are common causes of spontaneous miscarriages. Genetic testing is an integral part of diagnosing PWS with the use of advanced genetic technology and high-resolution chromosomal microarrays (see Fig. 1.3).

PWS and Angelman syndrome, an entirely different clinical disorder may often, due to a maternal deletion of the same 15q11–q13 region, were the first examples of genomic imprinting in humans, or the differential expression of genetic information depending on the parent of origin. Gene activity differences exist in both maternal and paternal chromosome 15s that impact the clinical phenotype or outcome. With at least 150 recognized imprinted genes in humans, or where gene activity depends on the parent of origin, often related to growth or development of the fetus [22].

There are three recognized subclasses of maternal disomy 15 (UPD15) based on the presence or absence of loss of heterozygosity (LOH) using SNP microarrays: maternal segmental isodisomy, maternal total isodisomy, and maternal heterodisomy. Maternal segmental isodisomy refers to segments of LOHs having identical genetic material (e.g., came from the same chromosome 15 in the mother during production of the egg), and maternal heterodisomy refers to the presence of genetic material from two different chromosome 15s received from the mother and

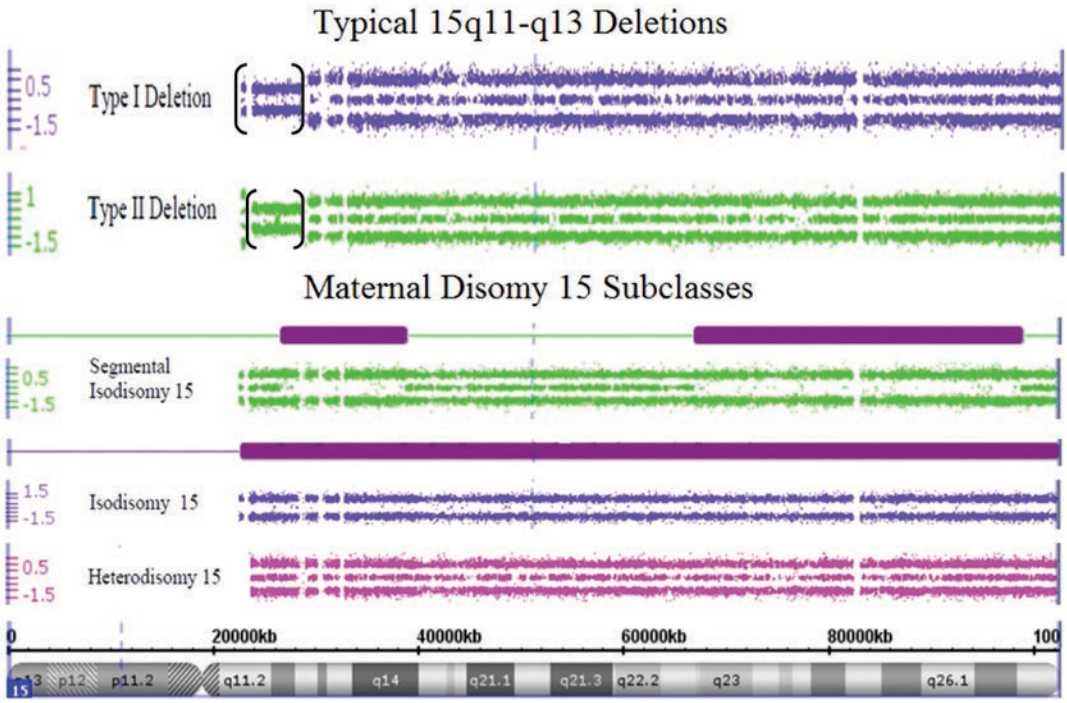

Fig. 1.3 High-resolution SNP microarray analysis of individuals with Prader-Willi syndrome showing the typical 15q11–q13 Type I deletion and smaller typical 15q11–q13 Type II deletion indicated with brackets. The three maternal disomy 15 subclasses are also illustrated based on the presence or absence of loss of heterozygosity determined by the size and location

without LOHs. Children with PWS due to maternal segmental isodisomy or total isodisomy 15 may be at increased risk of having a second genetic condition if the mother is a carrier of a recessive gene disorder on her chromosome 15 such as Bloom syndrome when the gene is located in the isodisomic region on chromosome 15 (segmental isodisomy involving part of the chromosome or total isodisomy involving the entire chromosome). The chromosome 15 long arm is about 80 Mb in size and includes hundreds of genes, both dominant and recessive.

Bloom syndrome is an autosomal recessive condition where the gene is located outside of the proximal 15q11–q13 region seen in PWS, but both members of the gene pair (alleles) are abnormal. If the mother carries an abnormal gene allele for Bloom syndrome on one of her chromosome 15s, she is unaffected because the gene allele on her other chromosome 15 is normal. However, if the chromosome 15 region or segment containing the abnormal recessive gene allele for Bloom syndrome is donated to the child by the mother in an isodisomy fashion (i.e., both chromosome 15s contain the same identical genetic information or alleles), then PWS results as well as Bloom syndrome (see Fig. 1.3). As noted, maternal UPD15 subclasses (heterodisomy, segmental isodisomy, and total isodisomy) are identified by high-resolution SNP microarrays. Hence, total isodisomy results from an LOH of the entire chromosome 15 due to a meiosis II errors or later with monosomy rescue. Segmental isodisomy 15 results from crossover(s) in meiosis I, and heterodisomy 15 occurs when no crossover events are present. The average number of crossovers on chromosome 15 occurring in normal individuals in meiosis I is approximately 1.7. Segmental isodisomy results when the exchange of genetic information between chromosome 15 homologues occurs with nondisjunction. The SNP microarray non-deletion pattern for maternal heterodisomy 15 is the same as seen in normal (control) individuals. The UPD15 subclass may impact diagnosis and medical care surveillance for a second genetic condition in PWS, if the mother is a carrier of a recessive gene allele in the LOH region leading to two copies of the recessive allele as discussed with Bloom syndrome or for the *POLG* gene at chromosome 15q26.1 causing mitochondrial DNA depletion and health-related problems. Accurate molecular genetic diagnosis for medical management and preventive care is needed and a rationale for characterizing the PWS molecular classes.

High-resolution SNP microarrays can also be used to identify typical and atypical chromosome 15 deletions in PWS, and are informative in 70% of those with UPD15 (i.e., heterodisomy, segmental, or total isodisomy) and also identify about one-fourth of those with imprinting center defects in the remaining cases [19]. Therefore, data when extrapolated would account for 86% of individuals with PWS identified with a SNP microarray abnormality (see Fig. 1.3). Refining the specific genetic defect and defining mechanisms for disease development and progression would be important for genetic counseling, testing at-risk individuals, selection of prenatal testing protocols, and for better treatment options, existing or novel.

Clinical differences have been identified in those with PWS deletion subtypes and UPD15 subclasses. Those with segmental or total isodisomy 15 may be at greater risk for unusual clinical findings due to a second genetic disorder as described if the mother has a recessive or a low penetrant dominant gene allele in the region. A large LOH with more genes in the involved segment would increase the likelihood of atypical features or a second genetic condition, as approximately 600 protein-coding genes are found on chromosome 15 with 454 annotated in OMIM (www.omim.org) including 75 autosomal recessive, 44 autosomal dominant, and 125 genes for clinical disorders. With 80 Mb of DNA on chromosome 15 and an average LOH size of 25 Mb in those with maternal segmental isodisomy 15, then one would anticipate approximately 30% of the 600 genes or about 180 to be located in the segmental region and a risk for a second genetic condition besides PWS depending on the size of the LOH. Fortunately, humans carry only a very small number of recessive alleles that are abnormal.

PWS is thought to be due to a contiguous gene condition involving several genes, with over one dozen protein-coding genes or transcripts (*SNORDs*) mapped to the 15q11–q13 region with the majority being imprinted; most are paternally expressed (active) or maternally silent. Several of these genes and transcripts are candidates for causing features recognized in PWS including *SNURF-SNRPN*, *NDN*, *SNORDs*, *MKRN3*, and *MAGEL2*. The *SNRPN* (small nuclear ribonucleoprotein N) and a second protein coding sequence (*SNURF* or *SNRPN* upstream reading frame) are located in the 15q11–q13 region. Exons 4–10 of the complex bicistronic *SNURF-SNRPN* gene encode a core spliceosomal protein (SmN) involved in mRNA splicing in the brain, whereas exons 1–3 encode a 71-amino-acid protein enriched in arginine residues. A disruption of this complex locus and the imprinting center will cause loss of function of paternally expressed genes in this region, leading to PWS. Multiple copies of paternally expressed noncoding C/D box snoRNAs or *SNORDs* involved in RNA processing are embedded within the long *SNURF-SNRPN* transcript. These include *SNORD107*, *SNORD64*, *SNORD116*, *SNORD115*, and *SNORD109B* [23]. Deletions of *SNORDs* may play a role in causing a PWS phenotype reported rarely in the literature, specifically *SNORD116* [24]. Other imprinted genes that are not components of the *SNURF-SNRPN* gene complex locus and located proximally are *MKRN3*, *MAGEL2*, *NDN*, and *NPAP1* involved in brain development and function. Several are known to cause a genetic condition when mutated (e.g., Schaaf-Yang syndrome, *MAGEL2* [25], and central precocious puberty 2, *MRKN3*) [26].

Necdin (*NDN*) is a paternally expressed gene in the brain and from the melanoma-associated protein (MAGE) family required for cell cycle proliferation and differentiation. It is suggested to play a role in brain development and axon growth. The *MAGEL2* gene is also paternally expressed in various brain regions including the hypothalamus. It plays a role in circadian rhythm, brain structure, and behavior associated with autism. Patients have been reported with the Schaaf-Yang syndrome when this gene is disturbed paternally and the *MKRN3* gene encodes a specific group of proteins (makorins) abundantly expressed (paternally) in the developing brain and nervous system. It may play a role in precocious puberty when disturbed.

Three gamma-aminobutyric acid (GABA) receptor subunit genes (*GABRB3*, *GABRA5*, and *GABRG3*) which are not imprinted are present in the distal 15q11–q13 region. The disturbances of receptor subunit genes for GABA, a major inhibitory neurotransmitter, have been implicated in a number of symptoms associated with PWS including hunger, obsessive-compulsive disorder, and altered visual perception and memory. The OCA2 gene encodes a protein for pigment production and distribution is located in the distal end of the chromosome 15q11–q13 region with equal expression from both parents. Gene mutations cause oculocutaneous albinism 2.

The *UBE3A* and *ATP10A* genes are located distal to the *SNURF-SNRPN* complex gene locus and imprinted with maternal expression only. A maternal deletion of the 15q11–q13 region or mutations of the *UBE3A* gene causes Angelman syndrome (AS). The *HERC2* gene is located at the chromosome 15q11–q13 distal breakpoint BP3, and *HERC2* pseudogenes are located at the proximal breakpoints BP1 and BP2. These repetitive DNA sequences are located at the site of breakage, leading to the larger typical Type I deletion between BP1 and BP3 and the smaller Type II deletion between BP2 and BP3 both PWS and AS but of different parent of origin. The loss of only the 15q11.2 BP1-BP2 region in a deletion form is now an emerging disorder (Burnside-Butler syndrome) identified using high-resolution microarrays [27]. It is characterized with a neurodevelopmental-autism phenotype and the most common genetic defect in patients presenting for genetic services with autism spectrum disorder (ASD) and other related conditions [16, 17]. The gene order and location can be seen in Fig. 1.4.

PWS and Angelman syndrome were the first examples of errors in genomic imprinting causing disease in humans. It is now recognized that

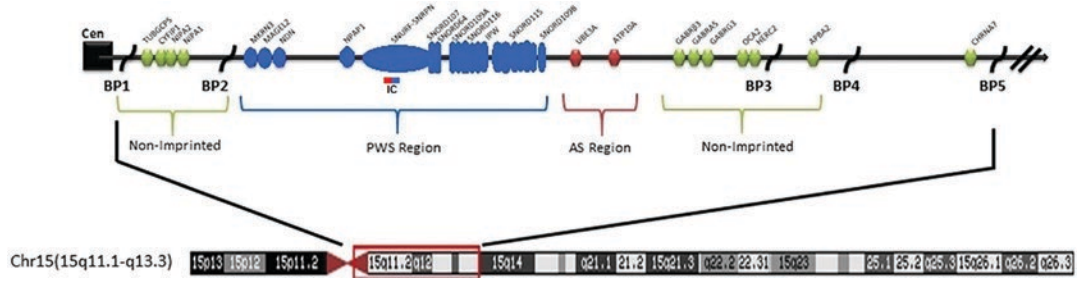

Fig. 1.4 Ideogram of chromosome 15 showing the order and location of genes and transcripts from the proximal long arm. Those implicated in causing Prader-Willi syndrome (PWS) are imprinted and paternally expressed (blue), and those in Angelman syndrome (AS) are imprinted and maternally expressed (red). The 15q11.2 BP1-BP2 deletion (Burnside-Butler) syndrome, typical larger 15q11–q13 Type I deletion involving breakpoints BP1 and BP3, and typical smaller 15q1-q13 Type II deletion involving breakpoints BP2 and BP3 and their location with breakpoints BP4 and BP5 distal to BP3 shown. IC: Imprinting center location controlling the activity of imprinted genes in the 15q11-q14 region involving PWS and AS

multiple syndromes affect growth, for example, Beckwith-Wiedemann syndrome with overgrowth and Silver-Russell syndrome with growth retardation due to errors in genomic imprinting. About 1% of human genes are imprinted; many encode growth factors or related proteins, and their receptors expressed on only one chromosome depending on the parent of origin. Paternally expressed imprinted genes are thought to enhance the growth of the fetus, while maternally expressed imprinted genes are more likely to inhibit growth. Genomic imprinting is now thought to play a role in other diseases such as malignancies, diabetes, and the aging process related to the methylation of cytosine bases in the CpG dinucleotides of the DNA molecule which are key regulatory elements of genes. Almost all imprinted genes have a CpG-rich differentially methylated region (DMR) which may often, relates to allele repression that is reversible. Many imprinted genes are arranged in clusters (imprinted domains) on different chromosomes under control of an imprinting center affecting animal growth, development, and viability. The phenomena of genomic imprinting with abnormal imprinting and loss of heterozygosity also contributes to a wide range of malignancies. The expression of imprinted genes may be tissue and stage specific with one of the parental alleles being differentially expressed only at a certain developmental stage or in certain cells. However, the monoallelic expression of an imprinted gene is not absolute. Thus, a potential role of genomic imprinting in the differentiation of tissue types may be to determine the transcription rate of genes that influence growth through a fine balance between the expression of the two parental alleles [22, 28].

Clinical Presentation and Diagnosis

Many clinical features in PWS may be subtle or nonspecific, while other features are more characteristic for the disorder. The primary features of PWS include infantile hypotonia, feeding difficulties, intellectual disability, hypogonadism, behavior problems (temper tantrums, stubbornness, obsessive-compulsive disorder), hyperphagia and early childhood onset of obesity, small hands and feet, endocrine disturbances including recently identified growth hormone deficiency, and a characteristic facial appearance (small upturned nose, narrow bifrontal diameter, dolichocephaly, down-turned corners of the mouth, sticky saliva, almond-shaped eyes, and strabismus) (Fig. 1.5). Table 1.1 lists the clinical manifestations, frequency, and time period when they occur. Some of the characteristics are subtle but well recognized by clinical geneticists trained in dysmorphology; however, a greater awareness by pediatricians, other physicians, and health care

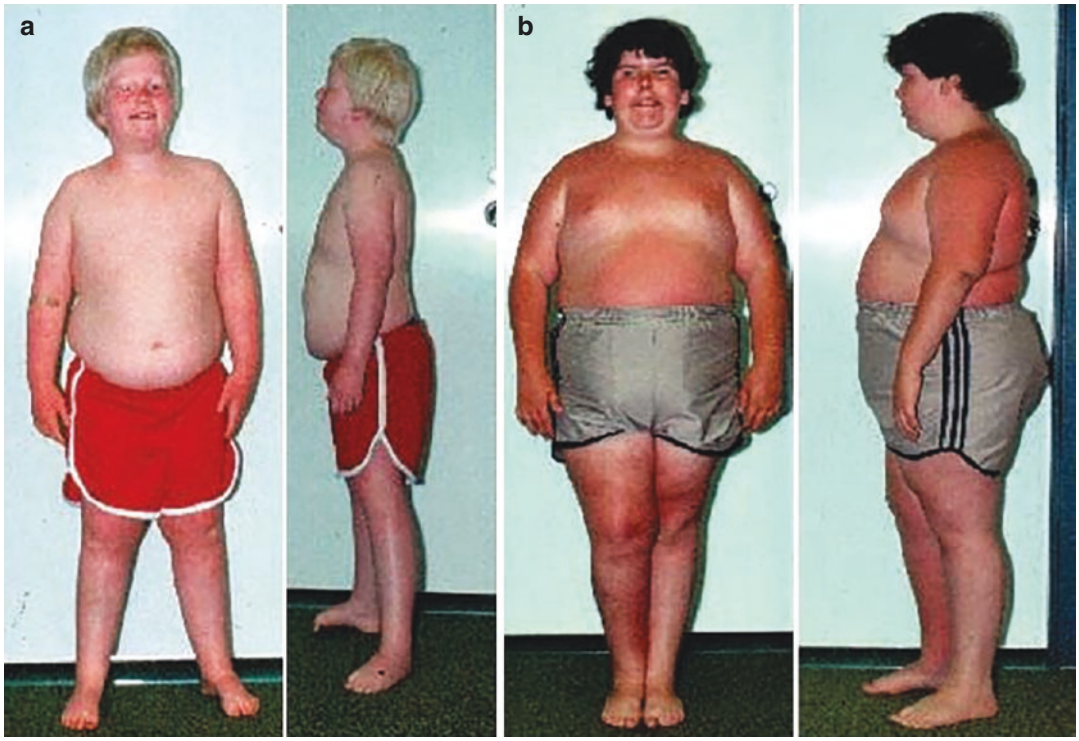

Fig. 1.5 Frontal and profile views of two males with Prader-Willi syndrome (patient A is 8.5 years of age with the chromosome 15q11–q13 deletion (seen in Fig. 1.1); patient B is 11 years of age with maternal disomy 15). Note the typical facial appearance (e.g., narrow bifrontal diameter, almond-shaped eyes, triangular mouth); small hands and feet with characteristic obesity are seen in both patients, but hypopigmentation is seen in patient A with the 15q11–q13 deletion. (Modified from Butler [2])

providers now exists. Because of the better recognition and awareness of PWS by the medical community during the past 10 years and more accurate and reliable genetic testing, the diagnosis is made earlier than in the past and extensive diagnostic procedures avoided. Many children with PWS were not diagnosed in the past until rapid weight gain leading to obesity was evident and the presence of specific learning/behavioral problems was observed. For example, in 1990, Butler [2] reported that the average age at diagnosis for PWS was greater than 6 years of age.

In 1993, Holm et al. [29] developed consensual original diagnostic criteria to assist in the diagnosis of PWS using major and minor features and established a scoring system for patients presenting with features seen in this syndrome. The scoring system consisted of three categories (major, minor, and supportive criteria), and scoring was based on a point system. The major criteria were weighed at one point each, while minor criteria were weighed at one-half point each. Supportive criteria received no points but may be helpful to confirm the diagnosis. Individuals can present with obesity and other features of PWS. These obesity-related genetic conditions will be illustrated and described in Chap. 2.

A testing strategy may follow consensus diagnostic criteria established in the past [29] for PWS based on clinical presentation in order to pursue genetic testing available from certified and licensed commercial laboratories to genetically confirm the diagnosis when suspected on clinical grounds. Early diagnosis in infancy is important for adequate and appropriate treat-

Table 1.1 Summary of clinical findings in individuals reported with Prader-Willi syndrome[a]

Time period when clinical manifestations first appear	Clinical manifestation	Affected/total Overall patients	(%)
Pregnancy and delivery	Reduced fetal activity	137/181	76
	Nonterm delivery	83/203	41
	Breech presentation	56/212	26
Neonatal and infancy	Delayed milestones	405/412	98
	Hypogenitalism/hypogonadism	270/285	95
	Hypotonia	504/538	94
	Feeding problems	445/479	93
	Cryptorchidism	240/273	88
	Narrow bifrontal diameter	138/184	75
	Low birth weight (<2.27 kg)	68/226	30
Childhood	Intellectual disability	504/517	97
	Obesity	287/306	94
	Small hands and feet	237/286	83
	Skin picking	261/330	79
	Short stature (<−1 SD)	232/306	76
	Almond-shaped eyes	151/202	25
	Strabismus	259/494	52
	Delayed bone age	74/148	50
	Scoliosis	159/360	44
	Personality problems	161/397	41
	Early dental caries/enamel hypoplasia	56/141	40
Adolescence and adulthood	Menstruation	38/98	39
	Reduced glucose tolerance/diabetes mellitus	74/371	20
	Seizures	40/199	20

Adapted from Butler [2]
[a]Number of males 286; number of females 211

ment. Molecular testing should include DNA methylation analysis and detection of the chromosome 15 deletion or other anomalies (see Table 1.1). The clinical findings that may prompt genetic testing for PWS classified by age include birth to age 2 years with hypotonia with a poor suck and feeding problems with inadequate weight gain; ages 2–6 years with a history of congenital central hypotonia, a poor suck, and global developmental delay; ages 6–12 years with a history of hypotonia with a poor suck, global developmental delay, food foraging with hyperphagia, and central obesity; and ages 13 years through adulthood with cognitive impairment, preoccupation with food, hyperphagia and central obesity, behavioral problems (e.g., temper tantrums, self-injury), and hypogonadotropic hypogonadism. Molecular testing for those with features of PWS should begin with DNA methylation analysis of blood, but methylation status will not identify the specific genetic cause. If the DNA methylation test is normal, then other clinical disorders should be considered using advanced genetic technology [30].

Personalized medicine based on pharmacogenetics testing is also a growing field for new genetic testing with a role in medication selection and management in the clinical setting for PWS. Pharmacogenetics is the study of inherited genetic differences in drug metabolic pathways impacting therapy with potential side effects based on specific genes encoding proteins required for drug metabolism involving the cytochrome (CYP) P450 hepatic enzymes [31, 32]. Identified pharmacodynamic genetic factors such as neurotransmitters and transporter gene polymorphisms can also be identified and inform psychotropic medication response in PWS.

Multiauthored documents by experts in genetics, diagnosis, psychiatry, and medical care with

PWS treatment approaches have been published for use in the clinical setting [30, 33]. One report was based on a searchable bulleted format of terms related to clinical and genetic background information for clinicians covering topics about Prader-Willi syndrome with recommendations for diagnosis, genetic testing, and treatment to guide clinical practice supported by evidence-based medical knowledge and syndrome-specific health care guidelines [30]. Early diagnosis is stressed and highlighted for use by a multidisciplinary team approach. Clinical presentation and list of features, genetic causation in PWS with counseling, diagnostic testing assays, and therapeutic management approaches are described including intervention and medication use for problems most commonly seen in this disorder [30, 32, 33]. A summary of clinical findings in individuals with PWS are described in Table 1.2.

Laboratory approaches with cytogenetic testing for PWS included fluorescence in situ hybridization (FISH) of chromosome 15q11–q13 DNA probes in the 1990s helpful in detecting deletions (Fig. 1.6). If the DNA probes isolated from the 15q11–q13 region did not hybridize, or attach, to a chromosome region, then the deletion status was confirmed. These studies showed that 70% of subjects with PWS had the typical chromosome 15q11–q13 deletion (Fig. 1.1), while about 25% had normal-appearing chromosomes. These methods have been replaced with newer genetic technology to identify the typical (i.e., larger 15q11–q13 Type I or smaller Type II) or atypical

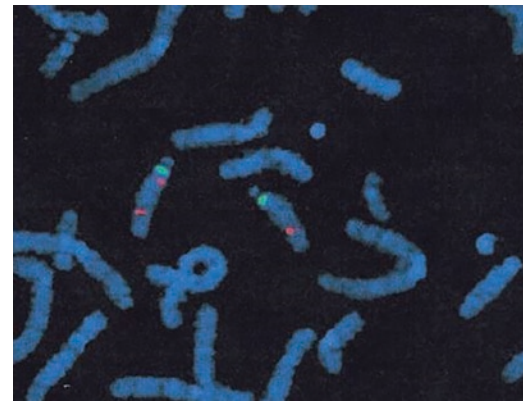

Fig. 1.6 Representative fluorescence in situ hybridization (FISH) using a SNRPN probe from the chromosome 15q11–q13 region (red color), a centromeric probe from chromosome 15 (green color), and a distal control probe from chromosome 15q (red color) showing the absence of the SNPRN signal close to the centromere on the deleted chromosome 15 from a subject with Prader-Willi syndrome

Table 1.2 Genetic laboratory testing for those presenting with features of Prader-Willi syndrome

1. DNA methylation testing of SNRPN gene with polymerase chain reaction (PCR) or Southern hybridization and/or MS-MLPA chromosome 15 testing If normal (unlikely PWS as DNA methylation is 99% accurate), then perform chromosome analysis to rule out translocations; consider other obesity-related disorders such as fragile X syndrome, and undergo clinical genetic evaluation and testing with next-generation sequencing for candidate gene variants If abnormal DNA methylation PWS pattern is seen, then undertake high-resolution SNP microarrays, FISH, MS-MLPA testing, and/or ddPCR with chromosome 15 probes to identify chromosome 15q deletions in PWS. Only SNP microarrays can identify maternal segmental isodisomy or total isodisomy 15 patterns in PWS as well as typical 15q11–q13 Type I or Type II deletions or atypical larger or smaller 15q deletions
2. If a nondeletion chromosome 15 finding is present by SNP microarray analysis, then either due to maternal heterodisomy 15 or an imprinting center defect (microdeletion or epimutation) requiring additional testing such as chromosome 15 genotyping
3. Parental and PWS child chromosome 15 polymorphic DNA testing will be required to identify biparental (normal) inheritance of chromosome 15 in those with a DNA methylation PWS pattern and nondeletion status without maternal segmental isodisomy 15 or total isodisomy 15 by SNP microarray analysis. DNA microsatellite analysis using PCR to confirm a paternal 15q11–q13 deletion and size (Type I or Type II) in PWS is needed to identify maternal disomy 15; DNA from the PWS child and each parent will be required
4. If biparental (normal) inheritance is found, then perform MS-MLPA (if not done) or other techniques such as ddPCR using chromosome 15 probes helpful in identifying microdeletions and mosaicism. If no microdeletion of the imprinting center is found, then this would support an epimutation with a low level of recurrence (<1%). If a microdeletion is seen in the father and in the PWS child, then the recurrence risk is 50% for having future children with PWS

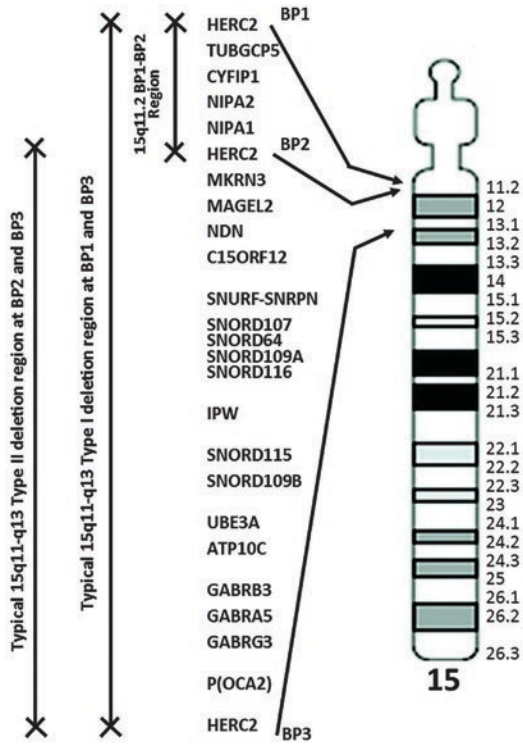

Fig. 1.7 Chromosome 15 ideogram, genes, and transcripts in the 15q11–q13 region showing the larger 15q11–q13 Type I deletion involving breakpoints BP1 and BP3 and the smaller Type II deletion involving breakpoints BP2 and BP3 seen in Prader-Willi syndrome and the 15q11.2 BP1-BP2 deletion seen in Burnside-Butler syndrome

(smaller or larger) deletions (Fig. 1.7). Additionally, maternal disomy 15 subclasses or imprinting center microdeletions using high-resolution SNP microarrays [19] or methylation-specific multiple ligation probe amplification (MS-MLPA) of chromosome 15 markers and control probes outside of 15q11–q13 region are used for methylation and deletion status of imprinted genes to identify both 15q11–q13 deletions and PWS methylation patterns [34]. All three genetic causes (deletion, maternal disomy, and imprinting defects) have abnormal methylation testing, but the specific types are not identified. Other rare genetic causes include translocations or inversions involving the chromosome 15q11–q13 region. Currently, DNA tests of children with PWS and normal-appearing chromosomes by FISH studies may often, have maternal disomy 15, or UPD15, using SNP chromosome microarray analysis. A small percentage (about 4%) will show normal (biparental) chromosome 15 inheritance with either small atypical deletions may often, undetectable with FISH or other defects such as microdeletions of the imprinting center. Table 1.2 lists genetic testing available to identify the genetic cause in PWS subjects. Molecular and cytogenetic testing for this syndrome will be described in more detail elsewhere in the textbook.

Clinical Stages, Nutritional Phases, and Natural History

Clinical Stages in PWS

The course and early natural history of PWS can be divided into two distinct clinical stages. The first stage occurs during the neonatal and early infancy periods and is characterized by varying degrees of hypotonia, a weak cry, a narrow forehead, developmental delay, temperature instability, a poor suck reflex, sticky saliva, feeding difficulties sometimes requiring gastrostomy or stomach tube placement, hypogonadism, and underdevelopment of the sex organs. Failure to thrive is noted during this first stage. The hypotonia is thought to be central in origin, nonprogressive, and on the average begins to improve between 8 and 11 months of age [13]. Infants with PWS sit independently at 11–12 months, crawl at 15–16 months, walk at 24–27 months, and talk (ten words) at 38–39 months. The delay in achieving motor milestones appears to relate more to psychomotor development than to excessive obesity. Language appears to be the most delayed of the developmental milestones [13, 35].

The second stage may often, begins around 2 years of age and is characterized by continued developmental delay or psychomotor retardation and onset of hyperphagia leading to obesity. Other features noted during the second stage may include speech articulation problems, foraging

for food, rumination, unmotivated sleepiness (found in greater than 50% of subjects), physical inactivity, decreased pain sensitivity, skin picking and other forms of self-injurious behavior, prolonged periods of hypothermia, strabismus, hypopigmentation, scoliosis, obstructive sleep apnea, and abnormal oral pathology (enamel hypoplasia, dental caries, malocclusion, and decreased saliva) [1].

Early in the second stage, infants and toddlers are may often, easy-going and affectionate, but personality problems develop between 3 and 5 years of age in about one-half of PWS individuals. Temper tantrums, depression, stubbornness, obsessive compulsivity, and sudden acts of violence of varying degrees may be observed during this stage. These behavioral changes may be initiated by withholding of food but may occur with little provocation during adolescence or young adulthood. Poor peer interactions, immaturity, and inappropriate social behavior may also occur during this time [2, 36–40].

Nutritional Phases in PWS

PWS has two recognized clinical stages noted including failure to thrive followed by hyperphagia that leads to obesity in early childhood, if not controlled externally. Recent classification and studies based on natural history have generated five proposed main nutritional phases that are highlighted by gradual progression of this disorder. The phases are as follows: Phase 0 occurring in utero with decreased fetal movement and growth failure; Phase 1 occurring with hypotonia and non-obesity from birth to 15 months; Subphase 1a with noted difficulty in feeding with or without failure to thrive; Subphase 1b with a steady infant growth rate and weight gain; Phase 2 with weight gains beginning at about 2 years of age; Subphase 2a with weight increases without change in appetite or caloric intake; Subphase 2b with weight gain occurring with an increased interest in food; Phase 3 with hyperphagia and lack of satiety accompanied by food seeking at about 8 years of age; and Phase 4 noted when appetite is no longer insatiable [41].

Natural History in PWS

Pregnancy and Delivery

Decreased fetal movement is noted by the mothers in nearly all PWS pregnancies. About one-fourth of babies with PWS are delivered in breech presentation. Approximately one-half of babies with PWS are born pre- or post-term (2 weeks earlier or later than the anticipated delivery date). Mild prenatal growth retardation is noted, with an average birth weight of 2.8 kg. Low birth weight is seen in about 30% of deliveries [2].

Infancy

Because of generalized hypotonia, neonates with PWS are profoundly floppy and their presentation can be mistaken for other disorders such as Werdnig-Hoffman or trisomy 18 syndromes, a brain anomaly or bleeding, a metabolic disturbance, an infectious agent, or other environmental insult. The hypotonia may lead to asphyxia and, in the past, has led to extensive medical evaluations including muscle biopsies and repeated brain imaging studies. Most of the structural brain imaging studies and muscle biopsies performed on infants are thought to be normal or not diagnostic for a specific syndrome.

Most infants with PWS have a weak or absent cry, little spontaneous movement, hyporeflexia, excessive sleepiness, and poor feeding due to diminished swallowing and sucking reflexes that may necessitate gavage feedings lasting for several months. However, feeding difficulties may often, improve by 6 months of age. Failure to thrive and poor weight gain are common features seen in infants with PWS. Due to failure to thrive, feeding difficulties, and hormone deficiencies, the growth of the PWS infant may fall below the third centile for weight. Temperature instability may be present during early infancy with high or low body temperatures. The bouts of hyperthermia or fever may trigger medical investigations to pursue an infectious agent, which is not often found. Infants with PWS have significant respiratory abnormalities including sleep-related central and obstructive apneas and reduced response to changes in oxygen and carbon dioxide levels [42–44]. PWS subjects tend to be relatively

insensitive to pain including that caused by obtaining blood samples. Cryptorchidism (undescended testicles) and a hypoplastic penis and scrotum are frequently seen in males and hypogenitalism in females. Cryptorchidism may require treatment (hormonal and/or surgery), and a referral to a pediatric urologist is warranted. In addition, the hands and feet may be small at birth.

Mild dysmorphic features are recognized during the infancy period, particularly involving the face. These features include a narrow forehead; mild upward slanting of the palpebral fissures; a long, narrow-appearing head (dolichocephaly); a small upturned nose; a thin upper lip; sticky saliva; and down-turned corners of the mouth. Many of the dysmorphic facial features are reminiscent of those due to midline central nervous system defects, while others such as a triangular mouth may be related to hypotonia and poor prenatal neuromuscular functioning. PWS subjects may have diminished facial mimic activity due to the muscular hypotonia as they grow older. They may also present with hypopigmentation for their family background, including fair skin and light hair color noted during the infancy period. Hypopigmentation relative to family background is a feature in about three-fourths of PWS subjects and correlates with those individuals having the 15q11–q13 deletion and loss of the *P* gene (which causes oculocutaneous albinism Type 2) located in this region [15].

As noted above, infants with PWS tend to sit at 11–12 months and crawl at 15–16 months on average. Developmental milestones are typically delayed, and the delay continues into childhood.

Early Childhood

Although infants with PWS may be tube-fed during infancy, by 18 months to 2 years of age, their feeding behavior changes radically, and an insatiable appetite may develop, which causes major somatic and psychological changes in early childhood. Along with global developmental delays, temper tantrums, difficulty in changing routines, stubbornness, controlling or manipulative behavior, and obsessive-compulsive behavior may become more apparent during childhood. Lying, stealing, and aggressive behavior are common during the childhood years and may continue into adolescence and adulthood. Children with PWS may be less agreeable, less open to new ideas and experiences, and more dependent than typically developing children. In addition, they are may often, less physically active than other children their age. Frequently, medical and/or behavior management advice is sought to treat the behavioral problems. Medications such as serotonin reuptake inhibitors have been of benefit in controlling behavior and psychiatric disturbances in some children with PWS, particularly as they become older [3, 5].

On average, toddlers with PWS learn to walk at about 27 months of age. By the time they enter kindergarten, they are nearly always overweight and short for age. However, growth hormone treatment significantly improves body composition, stature, and energy level. PWS children should be evaluated and treated for endocrine abnormalities such as hypothyroidism and growth retardation. In addition, enamel hypoplasia and dental caries are frequently seen during childhood in the syndrome. During early childhood PWS children may also develop nystagmus or strabismus, but the most common recognized eye finding in PWS is myopia [45], followed by decreased visual acuity and impaired stereoscopic vision; the latter finding is more common in PWS subjects with maternal disomy 15 and utilized with transcranial direct current stimulation when viewing food and nonfood images [46]. The hypopigmentation becomes more pronounced during childhood, particularly in those PWS subjects with the 15q11–q13 deletion.

The small hands and feet may not be apparent at birth but become more recognized during mid-childhood. Almond-shaped eyes may be more noticeable during childhood due to the periorbital tissue shape. A characteristic body habitus or posture, including sloping shoulders, heavy midsection, and genu valgus with straight lower leg borders and sparing of distal extremities from excess fat deposition, is may often, present by toddlerhood.

About one-third of children with PWS function in the low-normal intellectual range (70–100 IQ), and the remaining PWS children (and adults)

function in the mild-to-moderate range of intellectual disability (50–70 IQ) [1, 47]. The average IQ is 65, with a range of 20–100. Academic achievement is poor for cognitive ability. During the first 6 years of life, children with PWS often do not achieve normal levels of cognition, motor, or language development. There are reported differences in behavior, academic, and intelligence testing between the PWS subjects with the typical chromosome 15 deletion versus those with maternal disomy, which will be discussed later in this chapter. Many children with PWS begin school in mainstream settings. About 5% attend regular school until secondary level, but the intellectual impairment and potential behavioral problems present in the majority of children with the syndrome require special education and support services. By elementary school age, children with PWS may steal or hide food at home or during school to be eaten later. It is common for those with PWS to have relatively strong reading, visual, spatial, and long-term memory skills but relatively weak math, sequential processing, and short-term memory skills. Verbal skills are relative strengths, moreso in those PWS subjects with maternal disomy, although speech articulation is often poor, with nasal or slurred characteristics. An unusual skill with jigsaw puzzles and fine motor skills are particularly common in those with the typical 15q11–q13 deletion. Studies have documented genotype/phenotype differences between the two genetic subtypes (deletion vs maternal disomy), which may impact skills [18, 48, 49]. Additional psychobehavioral findings in children with PWS will be discussed in more depth elsewhere (see Chaps. 8 and 12).

Adolescence and Adulthood

Normal puberty is absent or delayed in both males and females with PWS and may be influenced by genetic factors [50]. Gonadotropin hormone production by the brain is low, and other endocrine disturbances may be identified in this subject population. As a result, adolescents and young adults with PWS look young for their chronologic age. The occurrence of reduced growth hormone secretion and hypogonadotropic hypogonadism in the majority of children and adolescents with PWS, along with an insatiable appetite and high pain threshold, would suggest a hypothalamic pituitary dysfunction.

Hypogonadism and hypogenitalism occur in the vast majority of males and females with PWS and become more evident during adolescence. The hypogonadism is due to hypothalamic hypogonadotropism, since it is often associated with low levels of gonadotropin released by the brain needed for gonadal development and function. The degree of hypogonadism is variable from patient to patient but more marked in males. Cryptorchidism occurs with a hypoplastic penis and scrotum in males and can be identified in early infancy, but the hypoplastic labia minora and clitoris in females may not be as easily recognized, although they are cardinal features of this syndrome. Sertoli cells and a variable number of Leydig and germinal cells are may often, present in the testicles, although there have been no reports of fertility in males. In addition, the tubules are may often, small and atrophic. Penile size increases modestly in many males during the third or fourth decade of life, but testicular size remains small. In males with palpable testes, the size is seldom greater than 6 ml in volume. Treatment of the small penis with topical or parenteral testosterone has been effective in achieving penile growth in PWS males [51]. However, mature genital development in males is rarely seen. Gonadotropin treatment may also be helpful in treating PWS males with cryptorchidism. Cryptorchid testes may descend spontaneously in some patients during childhood and puberty, but surgical intervention may be indicated. Precocious development of pubic and axillary hair occurs frequently as a consequence of premature adrenarche. The *MKRN3* imprinted gene in the PWS chromosome 15 critical region has been found to play a role in precocious puberty [26]. Beard and body hair are variable, occurring later than normal, if at all. Beard growth is absent in about 50% of men [52]. Additional endocrine-related findings and more in-depth discussions are presented in later chapters.

Menarche is often late or does not occur in females with PWS. In 98 appropriately aged females reported in the literature [2], 38 devel-

oped spontaneous menstruation (see Table 1.1). In a study of mostly adult PWS females, breast development was normal in about one-half, with onset between 9 and 13 years of age [35]. Primary amenorrhea (absence of menstruation) was found in about 70% of females and oligomenorrhea (infrequent menstruation) in the remaining. Age of menarche is extremely wide, from 7.5 to 38 years. In a series of 106 females between the ages of 15 and 63, 13 had been given hormones to induce menses. Very few of the women who had spontaneous menarche had regular menses; most had scant and infrequent menses [53]. Pubic hair was normal in 40% of females studied [35].

Women with presumed PWS were reported as early as the 1970s with established pregnancies. At least two women with documented genetically confirmed PWS have been reported more recently with established pregnancies. One woman with PWS was 33 years of age and had suspected maternal disomy (i.e., abnormal methylation testing and normal chromosome study with FISH). She gave birth to a healthy girl by C-section delivery after an estimated 41 weeks of gestation [54]. The other adult PWS female had the 15q deletion and gave birth, not surprisingly, to an infant with Angelman syndrome due to the child receiving the 15q deletion from its mother [55]. The mother with PWS and suspected maternal disomy had low cerebrospinal fluid concentration of 5-hydroxyindoleacetic acid, a serotonin metabolite [54]. Due to behavioral problems before pregnancy, she had been medically treated with serotonergic drugs, which may have influenced gonadotropin release to induce hormonal conditions required for pregnancy and possibly reflecting low serotonin synaptic transmission in the brain and influenced the importance of pharmacogenetic testing in PWS [32]. Warnock et al. [56] also reported onset of menses in two adult females with PWS when treated with fluoxetine, a serotonin reuptake inhibitor that increases the available serotonin for brain function. Therefore, fertility in women with PWS is exceedingly rare, but reproductive issues should be addressed in reproductive-age females with PWS. Undoubtedly, other females with PWS may had established pregnancies particularly with growth and other hormone replacement and behavioral medication use in common practice in both males and females with PWS.

Approximately 90% of subjects with PWS without growth hormone treatment will have short stature by adulthood. The average adult male without growth hormone therapy is 155 cm (61 inches) tall, and the adult female averages 147 cm (58 inches) [57]. Syndrome-specific standardized growth charts for PWS have been developed for use in the clinical setting for those with or without GH treatment [58–60]. These charts can be helpful for monitoring growth parameters in response to growth hormone treatment. Growth hormone treatment appears to normalize stature and markedly improves weight in PWS compared with standardized growth curves for non-growth hormone-treated PWS individuals. In addition, significantly higher IQ scores were found representing the vocabulary section of cognitive assessments (e.g., Stanford-Binet IQ tests) than those with PWS receiving growth hormone treatment in a pediatric-based study [61]. Growth hormone may also influence intelligence impacted by PWS genetic subtypes and possibly by age.

Growth standards for PWS from other countries have also been reported (see Appendix C) with growth hormone therapy increasing the growth spurt and impact positively on the ultimate height and body composition in PWS. Inverse correlations have been reported with linear measurements (e.g., height, hand and foot lengths) and age, indicating a deceleration of linear growth with increasing age relative to normal individuals [62]. A relative deceleration in growth of certain craniofacial dimensions (e.g., head circumference, head length) was also suggested [63]. Therefore, dolichocephaly or a long, narrow head shape may be considered an early diagnostic sign for PWS.

Small hands with thin, tapering fingers and small feet (acromicria) are seen during infancy and childhood and become more pronounced during adolescence and adulthood. There is a straight ulnar border of the hands. Foot length tends to be more affected than hand length, compared with normative standards. The average

adult shoe size for males not treated with growth hormone is size 5 and for female size 3.

Therefore, short stature and small hands and feet are present in the majority of PWS subjects, although the frequency in African-Americans is lower [64]. There is relative sparing of the hands and feet from obesity, with fat distribution often appearing to end abruptly at the ankle and wrist. Scoliosis may also become more pronounced during the adolescent period, and kyphosis may be present by early adulthood.

Orthopedic problems are first noted in PWS infants as hip dysplasia or subluxation (in 10% or higher) at birth or later in infancy with scoliosis appearing as bimodal with development prior to 4 years of age. This may often, occurs as infantile spinal curvature and later in childhood or early adolescence (in 40% or higher). About two-thirds of patients with PWS will be affected by the time of skeletal maturation may often, as lumbar or thoracolumbar curves in comparison with the general population having idiopathic scoliosis where the typical location is thoracic. Bracing or surgical intervention may be required, but osteoporosis and osteopenia are common leading to stress fractures and should be monitored. Adequate nutritional intake of calcium/vitamin D along with physical activity depending on the level of scoliosis will help in prevention. Growth hormone and sex steroid hormone deficiencies, commonly seen in this disorder, are contributing factors as well. Most patients with PWS have growth hormone deficiency and require GH treatment after genetic confirmation. Orthopedic complications should be monitored closely particularly during growth hormone treatment for short stature that also impacts positively on lean body mass, decrease fat, and improve physical activity. As these children may develop scoliosis as a component of this syndrome, radiological skeletal surveys for scoliosis should begin at about 18 months of age and monitored consistently [65].

Without intervention, adolescents with PWS may weigh 250–300 pounds by their late teens, which can lead to a shortened life from the complications of obesity. Overeating can lead to immediately life-threatening events such as stomach rupturing. By late adolescence, some with PWS begin stealing food from stores and rummaging through discarded lunch bags or trash cans to find partially eaten leftover food or inedible food items (e.g., bags of sugar, frozen food). Some parents find it necessary to lock the refrigerator and cabinets containing food to prevent excessive eating. Despite these precautions, youth with PWS may pry open locked cabinets to gain access to food. In the past, many patients with PWS died before the age of 30 years. The eating behavior, complications of obesity that can reduce the life expectancy of a person with PWS, and cognitive impairments will preclude normal adult independent living. Behavioral and psychiatric problems interfere with the quality of life in adulthood and may require medical treatment and behavioral management. However, if weight is adequately controlled, life expectancy may be normal. Hence, caloric diet restriction is lifelong and important to control the obesity and its complications. Continued consultation with a dietitian with experience in Prader-Willi syndrome is recommended [66].

Adults with PWS have generalized mild hypotonia and decreased muscle bulk and tone, poor coordination, and often decreased muscle strength. However, muscle electrophysiological and biopsy studies are may often, normal or nonspecific. The decreased muscle tone and muscle mass contribute to the lower metabolic rate, leading to physical inactivity and obesity, although thyroid function tests have may often, been within normal range but not adequately studied to date [2].

Sleep disorders and respiratory dysfunction such as hypoventilation and oxygen desaturation are common from childhood to adulthood for the PWS subject. Adolescents with PWS have a tendency to fall asleep during the day, particularly when they are inactive. They do not sleep soundly and may awaken often during the night; some may forage for food.

Behavioral and learning problems may become more prominent during the teenage years, particularly temper tantrums and obsessions. Typical adolescent rebelliousness is often exaggerated in those with PWS, particularly over

access to food. Psychotropic agents can be helpful in controlling abnormal behavior, but no specific medication has been universally effective in controlling abnormal behavior or food-seeking behavior. The use of medication to control behavior problems should be addressed [30, 32]. It should be noted that children and adults with PWS are typically affectionate and outgoing, like to please others, and seek positive attention.

Typical behavior problems in PWS include rigidity of personality, perseveration, tantrums, obsessive-compulsive symptoms, and noncompliance that may increase during adulthood with acute psychosis in young adulthood in about 10% of PWS patients. Maternal disomy 15 is associated with psychosis at a higher risk [67]. Earlier studies using brain imaging and neurophysiological screening (e.g., EEGs) have shown reduced processing speed related to sensory function and, in people with PWS and maternal disomy 15 compared in those with the 15q11–q13 deletion. Those with maternal disomy 15 have been reported with significantly increased reaction times compared to those with the deletion and healthy controls. However, deficits in specific brain regions identified by EEG tracings do relate to early modality or specific inhibition in N200 andP300 brain wave peaks, respectively. Specifically, those with the deletion subtype show impairment for only N200 modulation. Specific deficits in segregating human voices from a noise background with failure to fully process sensory information before initiation of a behavior-related response were greater in those with PWS and maternal disomy 15 compared with deletion [68].

Significantly reduced white matter brain microstructure was found in children with PWS mostly for the major white matter tracts in those with maternal disomy 15 compared to deletion, similarly seen in individuals without PWS but with schizophrenia. Brain networks have been analyzed in patients with schizophrenia including descriptions of brain connectivity suggesting a role for such impairments in the possible cause of psychosis [69]. This observation further suggests common brain mechanisms in those with specific PWS genetic subtypes and those without PWS but with psychosis and/or schizophrenia. Apparently, individuals with PWS and maternal disomy have a higher risk of developing psychosis particularly in early adulthood.

Mood disorders and the inability to control emotions and obsessions in PWS begin in early childhood and are at a high risk of developing psychosis in late adolescence or early adulthood, particularly in those with maternal disomy 15. They can have autistic traits requiring additional services and medication management in PWS. Furthermore, individuals with PWS present with delayed motor and language skills and mild learning disabilities with an average IQ of 65. Ongoing behavioral problems such as stubbornness, defiance, easy frustration, quickness to anger and outbursts, and self-injury are also common. More brain imaging and neurological studies are needed to characterize PWS and relationship to genetic subtypes and role of individual gene disturbances in the chromosome 15q11–q13 region, related genes, and genomic imprinting in PWS [70].

The adult with PWS may have goals for himself or herself similar to those of any other person entering adulthood: establishing vocational goals, deciding where to live, and desiring to become independent in decision-making. This sometimes leads to conflict and frequently causes an exacerbation of health and behavior problems. For most persons with PWS, formal education ends between ages 18 and 21 years. If vocational training has been successfully introduced before then, a smooth transition to the world can occur. Unfortunately, individuals may not have this available to them, and a gap exists between completion of school and entrance into a job-training program. This loss of daytime structured activities may often, results in behavioral deterioration, and health problems may occur or increase. The challenge to family members and caregivers is establishing an appropriate environment for the adult, which includes a supervised living arrangement (with food restrictions), a vocational setting appropriate for the skills and behavior of the young adult, and professional sources knowl-

edgeable about PWS. As in childhood, limiting access to food is essential, as is the skill in management of typical behavior problems. If this does not happen, deterioration in health occurs. Assignment of legal guardianship to another adult is frequently helpful and necessary to assure a safe environment for adults with PWS. Decisions regarding living arrangements and availability of food are may often, made unwisely by persons with the syndrome, and therefore it is in the best interest of the person to have guardianship legally assigned to a parent or other adult.

Some persons with PWS live into their seventh decade of life. A person who died at age 71 years was described in 1994 [71], and a second individual at 68 years of age was described in 2000 [72]. Several older persons with PWS are known to the PWS community and have not been reported in the literature. A review of causes of death in persons with PWS in 1996 indicated that obesity-hypoventilation syndrome caused the majority of deaths. This review included the experience of 7 physicians who cared for 665 persons with the syndrome [73]. Twenty-five deaths had occurred, 14 of them related to obesity complications and the remainder due to several other causes. The average age at death was 23 years. More recently causes of death in PWS were summarized from a total of 486 deaths from a 40-year mortality survey report from 1973 to 2015 with a mean age at death of 29.5 ± 16 years with 70% occurring in adulthood. Respiratory failure was the most common cause accounting for 31% of all deaths [74].

Recent research has shown that survival estimates for individuals with PWS have increased since 2000, the year growth hormone was approved for PWS treatment, especially with regard to cardiac deaths in females as well as thrombotic and gastrointestinal-related mortality [75]. Early diagnosis and better treatment plans including food security and growth hormone therapy with preventable measures have been described to avoid morbid obesity [30, 33] even raising the potential of newborn screening for PWS [76] to provide the earliest time for diagnosis and treatment including prenatal diagnosis using advanced genetic technology [77].

Obesity and Related Problems

Children with PWS become overweight by 2–4 years of age, without appropriate intervention, as a consequence of overeating due to an insatiable appetite and compulsive behavior related to food. Weight gain worsens over time due to the fact that individuals with PWS require fewer calories (40–70% reduction compared with nonobese controls), and it can become life-threatening, if not controlled. Historically, about one-third of subjects with PWS weigh more than 200% of their ideal body weight [78–80], and without an early diagnosis and intervention, significant morbidity and mortality may occur from the complications of obesity such as cardiopulmonary compromise. There is no approved medication treatment for hyperphagia and obesity in PWS, but clinical trials are underway and/or proposed to address this issue performed and will require more study (e.g., McCandless et al. [81]).

Specific obesity-related findings may be seen in PWS subjects including heart failure, hypertension, thrombophlebitis and chronic leg edema, orthopedic problems, abnormal lipid profiles, and type 2 diabetes mellitus. Premature development of atherosclerosis with severe coronary artery disease has been reported in PWS subjects [82]. Complications of obesity include skin rashes (particularly in fat folds), ulcers of the skin, and cellulitis (particularly in lower extremities). Other obesity-related problems may include obstructive sleep apnea and narrowing of the airway, pathologic fractures, reduced physical activity, impaired respiratory function and hypoventilation, high carbon dioxide levels, specific endocrine disturbances, risks from general anesthesia, and hypometabolism.

The primary health issues in PWS are exacerbated by obesity and related findings. When weight is kept under control, there are few serious health issues. If the weight increases, diseases associated with obesity may appear. For example, type 2 diabetes mellitus is seen in 25–30% of PWS adults who become morbidly obese [83]. Diabetes is difficult to control with medication if food restriction is inadequate. When food intake is reduced to the appropriate

number of calories, diabetes may often, comes under control quickly. Symptoms of the disease disappear in most cases, and blood sugar values become more normal. If this cannot be achieved, complications of diabetes may occur in a few years after the diabetes is detected. These complications may include retinopathy, neuropathy, kidney failure, and amputations. However, insulin resistance is lower in PWS subjects, and insulin sensitivity is higher compared with obese individuals without PWS [84].

Morbid obesity often causes obesity-related hypoventilation, which can be a serious problem and demands attention. Loud snoring, inability to sleep flat in bed, and shortness of breath with minimal exertion become noticeable. Hypoventilation and sleep apnea can reduce the oxygen level in the blood, necessitating pulmonary devices to increase oxygenation during sleep. If this is not reversed, right-sided heart failure (cor pulmonale) may ensue. Rapid weight gain, swelling of the ankles, marked shortness of breath, cyanosis, and decreased activity are signs of cardiac decompensation. Although rapid weight loss and a program of physical exercise can reverse this cascade of events, hospitalization may often, becomes necessary. A reevaluation of the living environment is essential when this occurs.

Appetite Regulation and Control

As previously stated, obesity is due to several factors such as hyperphagia and involvement of 30 recognized peptides generated peripherally that regulate eating behavior with 1of these (ghrelin) involved with increased eating. Furthermore, a lower metabolic rate, persistent hunger, decreased perception of satiety, and an uncontrollable appetite with impaired emesis are present in PWS [2, 51, 85]. The intense preoccupation with food, food craving, lack of satiation, and incessant food seeking in PWS are the most striking features of the syndrome. There are clinical reports of individuals with PWS engaging in pica and eating unpalatable food items (e.g., frozen food), although people with PWS may often, prefer the same foods as most other people, primarily sweet carbohydrates. It is also clear that they are willing to consume unpalatable items and even engage in pica when food access is sufficiently restricted.

Along with severe obesity, hyperphagia, hypogonadism, and GH deficiency and unlike individuals with common obesity, who have low fasting plasma ghrelin concentrations, those with PWS have high fasting-ghrelin concentrations. These high levels in PWS may contribute to hyperphagia. Hence, treatment with octreotide, a somatostatin agonist which decreases ghrelin concentrations in healthy and acromegalic adults and induces weight loss in children with hypothalamic obesity was performed in PWS, but body weight and composition, leptin, insulin, resting energy expenditure, and GH measures did not change. Further investigations may be warranted.

Hormones can also regulate appetite control [86, 87]. For example, ghrelin is an endogenous protein ligand for the GH secretagogue receptor in the brain that affects eating behavior. Infants with PWS as early as 3 months of age have high levels [88]. Ghrelin is a potent orexigenic enteric peptide produced by the stomach and implicated in short- and long-term regulation of appetite and body weight, as well as GH secretion [86–89]. Orexigenic effects of ghrelin are partially mediated via activation of anabolic neurons in the hypothalamic arcuate nucleus that co-expresses neuropeptide Y (NPY) and agouti-related protein (AGRP). Circulating ghrelin levels correlate negatively with body mass index (BMI) and are low in those with common obesity consistent with a compensatory rather than a causal role for ghrelin as noted in this condition, but ghrelin levels are reportedly increased in PWS beyond infancy [90].

PWS is a unique model for the study of appetite regulation and hyperphagia along with hypogonadism and hormone deficiencies as findings theorized to result from hypothalamic structure changes or dysfunction [91]. Relative to age and BMI-matched obese controls, children and adults with PWS have elevated fasting levels of ghrelin, a peptide that circulates as active (acylated) and inactive (desacylated) forms. An abnormal ratio

may play a role in the excessive eating pattern seen in PWS. Acylated ghrelin promotes food intake in humans and fat deposition with weight gain in experimental animals. The orexigenic effects of ghrelin may be opposed by peptide YY, an anorexigenic hormone secreted by the gastrointestinal tract in response to feeding. Both total and acyl ghrelin levels in healthy individuals fall after food intake. Through binding to the pituitary growth hormone secretagogue receptor (GHS-R), acyl ghrelin also stimulates GH secretion in normal weight children and adults under fasting conditions [92–96].

Phenotypic findings in animals receiving repeated central injections of NPY or AGRP include hyperphagia, obesity, GH dysregulation, and central hypogonadism. As PWS is the most common form of human syndromic obesity, hallmark features characteristically overlap with the predicted phenotype of NPY/AGRP neuron overactivation and may be compatible with ghrelin excess. Plasma ghrelin levels in PWS children and adults are three to five times higher than those in age and BMI-matched controls. While other forms of monogenic and polygenic obesity are associated with low ghrelin levels. Hence, hyperghrelinemia may play an important role in PWS including dysregulation of hypothalamic hormone secretion [97–99]. Ghrelin administration has been shown to suppress pulsatile LH secretion, impaired in PWS affecting slow-wave sleep patterns. There is evidence that ghrelin levels are lower after gastric bypass compared with obese controls.

PWS is associated with maladaptive social behavior, hyperphagia, and morbid obesity and neuropeptides playing a role such as orexin A, a hypothalamic neuropeptide important as a homeostatic regulator of feeding behavior and in energy metabolism via actions in the lateral hypothalamus. Dysregulation of orexin signaling could contribute to behavioral problems including hyperphagia in PWS. Therefore, morning fasting plasma orexin A levels were measured in a PWS child cohort relative to control children and analyzed using general linear model adjusting for diagnosis, gender, age, total body fat, and body mass index. Plasma orexin A levels were significantly higher in children with PWS compared with controls supporting that dysregulation of orexin signaling may contribute to behavioral problems and hyperphagia in PWS [100].

People with PWS have elevated plasma gamma aminobutyric acid (GABA) levels [101], possibly upregulated following loss of GABA receptor subunit genes from the chromosome 15q11–q13 region impacting other receptor subunits with resulting GABA-A receptor dysfunction. GABA acts as a major brain neurotransmitter involved with inhibition. GABA-ergic compounds may often, cause disinhibition, leading to even less impulse control [102]. People with PWS should have little impulse control when faced with availability of food, which is commonly claimed by parents and clinicians.

Only recently have studies investigated neuropeptide or endocrine factors contributing to eating behavior [94, 95]. For example, leptin produced by adipose tissue and cholecystokinin produced by the gut are mediators of satiety and eating behavior. However, no significant differences were found in fasting plasma levels for either leptin or cholecystokinin in PWS subjects compared with obese controls [99, 103–105]. In addition, no significant differences in plasma levels were found in the two PWS genetic subtypes (typical deletion and maternal disomy). It appears that leptin levels in PWS follow the pattern observed in the normal population and are positively correlated with fat mass.

Individuals with PWS show distinct abnormal behaviors including hyperphagia, profound social deficits, and obsessive-compulsive tendencies which may be impacted by deranged oxytocin biology as reduced oxytocin receptor gene expression and lower density in the hypothalamic paraventricular nucleus have been observed in PWS. Oxytocin is an anorexigenic neuropeptide similar to vasopressin and associated with social cognition and obsessive-compulsive behavior. In a study by Johnson et al. [106], oxytocin plasma levels were found to be significantly elevated at a twofold level in children with PWS compared with unrelated and unaffected siblings without PWS which may relate to the disruption of oxytocin responsivity or feedback in the hypothalamic

paraventricular nucleus possibly influencing vasopressin signaling. Oxytocin clinical trials have had both positive and negative findings indicating the need to continue with testing (e.g., Miller et al. [107]).

Fasting insulin levels and HOMA-IR are lower with higher adiponectin levels in children with PWS than in age and gender-matched obese controls. HOMA-IR is a measure of hepatic insulin sensitivity. Hypoinsulinemia, decreased HOMA-IR, and hyperadiponectinemia in PWS would suggest heightened insulin sensitivity along with relative hyperghrelinemia that may contribute to hyperphagia. To identify metabolic factors controlling appetite and insulin sensitivity in PWS and to assess the effects of GH treatment, Irizarry et al. [108] compared amino acids (specifically branched-chain amino acids – BCAA), fatty acids, and acylcarnitines levels in GH-treated and untreated PWS children with obese and lean controls ghrelin, peptide YY, and markers of insulin sensitivity such as adiponectin and HOMA-IR in obese and PWS children. Hyperghrelinemia, hyperadiponectinemia, hypoinsulinemia, and increased ghrelin/PYY levels were more often seen in PWS females than in males. GH-treated PWS subjects had lower leptin and higher IGF-1 and adiponectin levels than untreated subjects; however, ghrelin, PYY, and insulin levels were comparable. Ghrelin correlated inversely with BCAA in PWS, while adiponectin correlated negatively with BMIz measures and HOMA-IR in PWS in contrast to obese controls. Low BCAA in PWS females may promote hyperghrelinemia and hyperphagia, while hyperadiponectinemia may maintain insulin sensitivity despite excess weight gain. GH treatment may also reduce leptin and increase adiponectin, but does not affect ghrelin or PYY [108].

With the most striking symptom in PWS being hyperphagia, overeating, and obesity commonly seen in the general population, functional magnetic resonance imaging (fMRI) was used to study neural mechanisms underlying responses to visual food stimuli, before and after eating, in individuals with PWS and a healthy weight control (HWC) group. In a study reported by Holsen et al. [109], participants were scanned once before (pre-meal) and once after (post-meal) eating a standardized meal. Pictures of food, animals, and blurred control images were presented in a block design format during acquisition of functional magnetic resonance imaging data. Data analysis in the HWC group showed greater activation to food pictures in the pre-meal condition compared with the post-meal condition in the amygdala, orbitofrontal cortex, medial prefrontal cortex (medial PFC), and frontal operculum. However, those with PWS exhibited greater activation to food pictures in the post-meal condition compared with the pre-meal condition in the orbitofrontal cortex, medial PFC, insula, hippocampus, and parahippocampal gyrus indicating distinct neural mechanisms associated with hyperphagia in PWS. After eating a meal, the PWS group showed hyperfunction in limbic and paralimbic regions that drive eating behavior (e.g., the amygdala) and in regions that suppress food intake (e.g., the medial PFC).

Metabolism and Energy Expenditure

The morbid obesity associated with PWS is the result of chronic imbalance between energy intake and energy expenditure. It is challenging to objectively measure these two components of energy balance in PWS due to the mental and physical status of these patients, but this is essential to determine the energy expenditure per subject and specific treatment options. Preliminary studies in PWS have attempted to measure energy expenditure. For example, daily energy expenditure was reported to be 47% lower in PWS subjects compared with controls, but this difference was reduced to 14% when allowances were made for differences in fat-free mass. Basal or resting energy expenditure, corrected for fat-free mass, was similar in PWS patients compared with obese controls, suggesting that the low daily energy expenditure in PWS was mainly a result of a reduced fat-free mass (muscle) and possibly a lower level of physical activity. However, electromyograms, motor nerve conduction velocity tests, serum creatine phosphokinase, and results of light microscopy studies of muscles are may often,

normal in PWS [85], while specialized histochemistry studies of muscles demonstrate Type II muscle fiber atrophy consistent with disuse [110].

Decreased energy expenditure and possibly biochemical problems in PWS are thought to contribute to reduced muscle mass and physical activity. However, these findings may also relate to cellular metabolism and disturbances in mitochondrial function. To evaluate mitochondrial function in PWS, Butler et al. [111] examined living fibroblast cell lines in both children and adults with PWS and healthy controls for mitochondrial assays using Agilent Seahorse XF extracellular flux technology which determines real-time measurements of several metabolic parameters including cellular substrate utilization, adenosine triphosphate (ATP)-linked respiration, and mitochondrial capacity in living cells. These reported preliminary studies showed decreased mitochondrial function in PWS cells compared to healthy controls with lower basal respiration, maximal respiratory capacity, and ATP-linked respiration and if validated in a larger number of subjects would be important showing mitochondrial dysfunction as a contributing factor in causing significant features found in PWS.

Few metabolic studies have explained the obesity in PWS, particularly relating to adipose tissue metabolism as thyroid hormone, lipid profiles, glucocorticoid, and amino acid levels in PWS that are comparable to obese individuals without PWS, although reduced glucose tolerance is reported in one-fifth of patients with PWS [112–115]. While fat cells are found to be larger in PWS compared to control individuals, uptake of fat and fatty acid composition in adipose tissue was normal, and the fat cell number was not increased [116–118]. Levels of adipose tissue lipoprotein lipase, an enzyme that regulates uptake and storage of triglycerides, were increased tenfold in fat biopsy specimens from seven PWS subjects compared with those of control individuals, when adjusted for percent ideal body weight and fat cell size [119]. This enzyme may be elevated in PWS.

Serum cholesterol and triglyceride levels are may often, thought to be normal in PWS, but fat biopsy specimens reported from nine subjects with PWS showed that triglycerides make up more than 98% of the fat [120]. There was a demonstrated threefold increase in long-chain polyunsaturated fatty acids, which suggested a resistance to lipolysis or breakdown of fat. In addition, body composition and substrate utilization studies in 11 PWS subjects showed a higher percentage of adipose tissue, but an apparent normal substrate utilization was found with a normal percentage of fat used for basal metabolism when compared with other obese control individuals [120]. The roles of the elevated long-chain fatty acids and increased levels of adipose tissue lipase in the development of obesity in PWS suggested from fat biopsy specimens are not understood.

The muscle is a metabolically active tissue, while adipose or fat stores energy. Therefore, the low muscle mass in PWS significantly contributes to hypotonia, reduced physical activity, and low energy expenditure. These factors lead to storage of energy in the form of excess adipose tissue. In one study, PWS subjects expended approximately 50% less energy than healthy obese controls. Daily energy expenditure can be measured using a whole-room calorimeter to record oxygen utilization and carbon dioxide production to determine the metabolic rate and energy expenditure. Lower levels were found in PWS subjects compared with obese controls. However, no information was recorded for differences in fat-free mass or muscle [1].

Hill et al. [121] reported resting metabolic rates in lean, obese, and PWS subjects using indirect calorimetry following an overnight fast. The PWS subjects had the lowest resting metabolic rate, followed by lean then obese subjects. The usual strong relationship observed between resting energy expenditure and fat-free mass was not found in the children studied, compared with non-PWS lean and obese controls. The study further suggested that the initial low rates of energy expenditure in subjects with PWS was independent of fat-free mass, but once patients gained a large amount of weight, the relationship appeared to normalize. Goldstone et al. [122] reported on 13 women with PWS and 45 control women and also found differences in resting metabolic rate.

Such differences could be explained by the abnormal body composition in PWS.

Reduced physical activity described in PWS subjects was suggested by Schoeller et al. [80] as a major cause of the decreased energy expenditure requirements. Although subjects with PWS have hypotonia during infancy, which lessens during the first 1–2 years of life, a residual amount that remains throughout life. This low muscle tone and lack of coordination may favor a sedentary lifestyle. However, few studies have attempted to quantify the levels of physical activity in PWS either in a free setting or in a controlled institutional care setting. It is thought that children with PWS are less physically active during play compared with normal children. To assess physical activity, Nardella et al. [123] studied children with PWS and controls attending a summer camp over a 2-week period by using portable activity meters and pedometers. They reported a wide range of activity levels in subjects with PWS compared with normal children. These results were inconclusive and furthermore did not address the situation in a free setting.

The obesity in PWS is the result of a chronic imbalance between energy intake and energy expenditure (EE) related to hyperphagia, decreased physical activity, and a lower metabolic rate along with the inability to vomit. EE is affected by both body composition and exercise which further impacted by a lower lean body mass (LBM) in PWS compared with controls contributing to a reduced basal level EE. To determine the relationship among body composition, activity levels and metabolic rates and dual-energy X-ray absorptiometry (DEXA) and a whole-room respiration chamber were used to measure body composition, total EE (TEE), resting EE (REE), physical activity, and mechanical work (MW) during an 8-h monitoring period. The live-in whole-room indirect calorimeter was equipped with a force platform floor to allow simultaneous measurement of EE, physical activity, and work efficiency during spontaneous activities and standardized exercise. Forty-eight participants with PWS whom were 10 years and older had significantly decreased TEE by 20% and reduced LBM compared to 24 obese subjects. Similarly, REE and total MW performed during an 8-h monitoring period in the chamber were significantly reduced in the PWS group. Interestingly, Butler et al. [124] reported that after adjusting group differences in LBM by analysis of variance, both TEE and REE were no longer different between the PWS and control groups. This observation of thereby significant reduction of EE in individuals with PWS related to reduced activity and lower energy utilization due to reduced LBM consisting primarily of muscle.

The role of altered energy expenditure and decreased metabolic rate as the causation of obesity, along with excessive caloric intake, decreased energy expenditure, and reduced physical activity leading to morbid obesity in PWS subjects, will require additional research. Growth hormone deficiency and its therapeutic use to stimulate growth, particularly to increase stature and muscle mass while decreasing fat mass and improving pulmonary function in PWS subjects, will require further long-term studies, but significant benefits have been reported. Growth hormone therapy and related endocrine and metabolic issues will be described elsewhere.

Onset and Measurement of Obesity

The onset of obesity occurs between ages 1 and 6 years, depending on the definition of obesity, with an average age of onset by 2 years in PWS subjects without growth hormone treatment. This onset follows a period of failure to thrive, feeding difficulties, and hypotonia during the neonatal and early infancy period, which is designated as the first stage of PWS. The abnormal feeding noted during infancy may be due to central nervous system or brain dysfunction, particularly an abnormality of the hypothalamus, although gross neuropathologic studies have not identified a consistent brain lesion in this area. However, limited brain imaging studies with positron emission tomography for evaluating brain metabolism have indicated decreased glucose metabolism in the parietal lobes of the brain and hypothalamus

in at least one adult with PWS. In addition, recent studies have shown abnormal oxytocin levels in the brains of PWS subjects [125] and high plasma levels of GABA [101], which will require further testing.

Historically, skinfold measurements of PWS infants show excessive fat at an early age (6 months) and before the infant is judged to be obese by weight/length parameters. The subcutaneous fat pattern is characteristically centrally located over the buttocks, trunk, and thighs but spares the distal regions of the extremities [51, 78, 80]. A two- to threefold increased fat mass compared with the general population has been reported, using skinfold measurements to determine percent body fat [78]. This patterning has been substantiated using more current and accurate measures of obesity such as dual-energy X-ray absorptiometry (DXA); for example, 40–60% body fat was found using DXA in a recent study, which is about two- to threefold higher than in the general population [126]. There are several methods in use to determine body composition, particularly fat, such as bioelectrical impedance, which measures fat-free mass and fat mass; skinfold thickness, which measures subcutaneous fat mass at various sites; magnetic resonance imaging (MRI) of lean and fat tissues; and DXA (or DEXA), which provides a measure of fat tissue, lean tissue, and bone density. Of the methods listed, DXA is considered the most accurate in determining body composition in PWS or in healthy subjects.

To further characterize total and body composition and fatness patterns in PWS compared with simple obesity, Theodoro et al. [127] studied 72 individuals with PWS from 10 to 49 years of age using DXA imaging. Significant differences were found between PWS and obese subjects for lean measures of the arms, legs, and trunk along with total lean mass which were significantly lower in PWS than in obese subjects. No significant differences were identified between PWS deletion and those with maternal disomy. The results demonstrate that PWS individuals have an unusual body composition and fatness patterns, characterized by reduced lean tissue and increased adiposity, with PWS males contributing most with fat patterns and more similar to females.

Growth hormone (GH) replacement positively influences stature and body composition in PWS and presumably an early diagnosis delays onset of obesity in PWS. The age of diagnosis and ethnicity were significant factors influencing when PWS children first became heavy in a recent study, but gender and PWS molecular class had no influence [61]. An early diagnosis permits treatment with GH, better intervention with food security and monitoring caloric intake, and a reduced onset of becoming heavy in individuals with PWS and reduces the risk of obesity-associated comorbidities. Non-White individuals had an earlier onset of becoming heavy [61].

The fatness pattern in PWS appears sex-reversed, with males having more fat than females [78]. Historically, individuals with PWS were described as morbidly obese with body mass index (BMI, defined as weight in kilograms divided by height in meters squared in adults) reported as high as 47 ± 4.2, compared with a normal BMI range between 21 and 27 [112]. There is a tendency for internal or visceral fat areas, as determined by MRI studies, to be lower in PWS subjects compared with obese subjects, as reported by Goldstone et al. [128] in adult females with PWS and obese control women. Significantly reduced visceral fatness or adiposity were seen in the PWS females, independent of their total adiposity or use of exogenous sex steroid treatment. This was in contrast to that expected by their physical inactivity, hypogonadism, growth hormone deficiency, and psychiatric problems. However, Talebizadeh and Butler [84] also observed an overall trend for decreased visceral fat area but not significantly different in the PWS. They observed that PWS subjects with higher visceral fat area may be at an increased risk for obesity-related complications, compared with PWS subjects without an elevated visceral fat area. The cause of the reduced visceral adiposity in PWS may reflect hormone imbalance, hypothalamic dysfunction, or genetic influence on body fat distribution. The visceral fat is posi-

tively correlated with glucose and triglyceride levels in both PWS and obese subjects and contributes to insulin resistance. A different peripheral-visceral fat storage pattern seen in PWS subjects compared with obese controls may account for the abnormal fat storage and lipolysis in PWS.

Weight Management

Weight control through diet restriction, exercise programs, and/or hormone replacement is a constant key management issue throughout the life span of an individual with PWS. Diet is historically the cornerstone for controlling the obesity seen in PWS. Caloric restriction of 6–8 calories/cm of height will be required to allow for weight loss, while 10–12 calories/cm of height may often, maintains weight in children with PWS, particularly in those not undergoing growth hormone therapy [66].

Historically, the calorie requirement to maintain weight is about 60% of normal. A low-calorie, well-balanced diet of 1000–1200 kcal/day combined with regular exercise would be advised, but this is difficult to implement in children and adults with PWS due to the insatiable appetite and food-seeking behavior. Supplemental vitamins and calcium are recommended. Unfortunately, no medications or surgical procedures have had long-term effectiveness in controlling appetite and obesity in PWS. An exercise regime should also contribute to weight loss and may improve hypotonia, respiratory problems, and excessive daytime sleepiness and apnea common in PWS subjects. In addition, locking refrigerators and food cupboards may be required to prevent the person with PWS from obtaining additional food and from eating inappropriately. With the increasing use of growth hormone therapy in the pediatric PWS population, weight, stature, and food security with monitoring caloric intake require close supervision by a multidisciplinary team.

Since limited data exist on adults with Prader-Willi syndrome and without a previous history of growth hormone treatment, Butler et al. [129] reported on PWS adults with an average age of 32 years over a 2-year period with GH treatment during the first year. The total lean muscle mass was significantly increased during GH treatment along with moderate-vigorous physical activity and plasma IGF-I and HDL levels. However, these measures returned to near baseline after GH treatment during the first year. Percent body fat did decrease during the first year and also diminished to near baseline after cessation of GH treatment for 12 months supporting the continuation of treatment in PWS into adulthood.

Surgical procedures such as gastroplasty (reducing the size of the stomach) and intestinal bypass to correct or prevent obesity have met with only limited success in PWS. Stomach rupture has been reported as a cause of death in PWS due to overeating [73], and surgically decreasing the size of the stomach may further increase the risk for the stomach to rupture. Comorbidities associated with PWS such as respiratory problems/hypoventilation, diabetes, and stroke commonly seen in obese individuals and other findings including osteoporosis, growth hormone deficiency, and hypogonadism with altered pain threshold and inability to vomit do pose unique issues in the care and treatment of individuals with PWS. Various bariatric surgical procedures used in treating morbid obesity in the general population to decrease gastric volume and induce malabsorption have been met, with limited results in PWS patients [130]. Therefore, these surgical procedures are not recommended by PWS experts at this time in PWS.

As concluded, obesity is the most significant health problem in PWS and is an increasingly common trait affecting one-half of the general adult population in the United States [131, 132]. It is on the rise in children with dramatic increases and a risk factor in five of the top ten causes of death (heart disease, stroke, diabetes, atherosclerosis, and malignancies) in the United States. There are several genetic syndromes besides PWS with obesity as a major component. These include Cohen, Bardet-Biedl, Albright hereditary osteodystrophy, Borjeson-Forssman-Lehmann, Alstrom, Carpenter, and fragile X syndromes;

cytogenetic or chromosome syndromes (e.g., 1p36 deletion, Smith-Magenis syndrome, Down syndrome, sex chromosome aneuploidy); and mutations of several obesity-related genes (e.g., leptin, leptin receptor, melanocortin 4-receptor, pro-opiomelanocortin (POMC), prohormone convertase-I, peroxisome proliferator-activated receptor-gamma, and beta-3 adrenergic receptor) (e.g., Kaur et al. [133]). However, PWS is the best example of an obesity syndrome to study to gain a better understanding of the genetics of obesity, as well as behavioral dysfunction and genotype/phenotype correlations.

Other Medical Findings

Bone Density

Other health concerns in individuals with PWS include reduced bone density and osteoporosis, which may lead to fractures [126, 134, 135]. Bone mineral density is a function of a dynamic process of bone resorption and production of mineralized bone matrix. The degradation of bone matrix or collagen can be determined by measuring urinary N-telopeptides of Type I collagen, while total bone mineral content and body composition (e.g., percent fat) can be determined by dual-energy X-ray absorptiometry (DXA). Butler et al. [126] reported data on bone density, anthropometric measurements, and biochemical markers of bone turnover in subjects with PWS or simple obesity. Significantly decreased total bone and spine mineral density and total bone mineral content in PWS subjects (ages 10–44 years) were found compared with normative data and similarly aged controls. However, no significant difference in urinary N-telopeptide levels was found between the PWS subjects and obese controls. This suggested a possible lack of depositing bone mineral during growth, when bones should become more dense (e.g., in adolescence), more so than bone loss in the subjects with PWS. This may be due to decreased production of sex or growth hormones and/or long-standing hypotonia with decreased physical activity.

Oral and Dental Issues

Dental or oral findings have received limited study in PWS, but thick, sticky saliva is a consistent finding detectable during the neonatal period regardless of the genetic subtype. Therefore, the gene(s) causing the salivary problem may be influenced by genetic imprinting as salivary flow is approximately 20% of that reported in controls [136]. Xerostomia or a dry mouth is frequently seen in PWS subjects with salivary protein present in increased amounts, reflecting a concentration effect relative to decreased water in the saliva.

Normal salivation acts as a buffering capacity by induction of clearing of substances in the mouth by swallowing, protecting the teeth from extrinsic and intrinsic acids that lead to dental erosion. It allows for a capacity to remineralize partially demineralized enamel in individuals [137]. Salivary dysfunction as seen in PWS predisposes to tooth wear and the inability to protect teeth against wear by erosion, attrition, and abrasion. Dental malocclusion also occurs in varying degrees in PWS and may require orthodontic treatment. Altered craniofacial development with maxillary hypoplasia in PWS may also predispose to dental malocclusion and possibly a narrow upper airway. Hence, the importance of dental care is emphasized in PWS to monitor and treat the dental problems frequently seen.

Feeding difficulties are also present in PWS, but swallow physiology and related anatomical problems have not previously been studied. Swallow dysfunction increases risks of respiratory compromise and choking which are noted in PWS at a high rate. Swallow pathology in PWS infants was recently studied in a retrospective review of video fluoroscopic swallowing studies in infants with PWS in order to characterize swallow pathology during a feeding evaluation. A high rate of swallowing dysfunction (pharyngeal residue and aspiration events) was found and disordered sleep by polysomnography. All aspiration events were silent. No differences were found in rates of aspiration for gender, PWS genetic subtype, or GH use. A comprehensive evaluation of feeding and swallowing studies in

PWS infants are essential and requires a multidisciplinary approach [138].

Growth and Growth Hormone

Growth in people with PWS is may often, characterized by initial failure to thrive, which may require gavage or tube-feeding during stage one of development, followed by a period of normal growth rate with heights below the 50th centile and often below the 10th centile. The lack of a growth spurt during adolescence results ultimately in mild short stature in both males and females. Without growth hormone treatment, adult males with PWS are may often, no taller than typical females in relationship to normative data. Bone age is may often, delayed but may be normal or advanced. However, observed delays or accelerations of bone age may often, return toward normal during adolescence or adulthood.

Intrafamilial and midparental PWS correlations and heritability estimates of anthropometric or physical variables from PWS subjects and their parents were undertaken by Butler et al. [139] in order to determine the effects of the genetic background on several growth parameters in this syndrome. The data suggested that taller parents with longer foot length have taller-than-average PWS children with longer feet. These physical characteristics are apparently influenced by the genetic background, while soft tissue parameters such as arm and calf circumferences and skinfolds showed lower heritability estimates.

Growth hormone deficiency or insufficiency is now recognized as a key feature of PWS and will be discussed in major detail elsewhere. However, one study of children with PWS showed that 98% had subnormal growth hormone levels over a 24-h period, and 91% displayed subnormal response to growth hormone stimulation [140]. This insufficiency affects both stature and body composition in PWS subjects. Individuals with simple obesity without PWS also show reduced growth hormone secretion during provocative testing when compared with nonobese subjects, but the growth hormone insufficiency in PWS is not considered to be secondary to obesity. Individuals with simple obesity tend to be taller than normal due to elevated levels of another growth-promoting protein produced by the liver called insulin-like growth factor I (IGF-I) [141]. IGF-I is low in children with PWS [142, 143].

Recombinant human GH therapy in PWS was approved in the United States in 2000 and in Europe in 2001 for focused attention to increase height. Deal et al. [144] reported recommendations for the use of GH in children and adults with PWS by performing a systematic review of the clinical evidence and safety data with input from international experts. Clinical outcome priorities varied depending upon age and level of disabilities, but treatment should be continued for as long as demonstrated benefits outweigh risks [144].

Their studies consistently showed that GH treatment improves stature, body composition, fat percentage and distribution, and other metabolic markers in children with PWS. Preliminary reports of improved cognitive development during GH have also emerged [145]. Additionally, scoliosis progression is influenced by growth rate, but the frequency of occurrence and severity are not increased by GH exposure, and PWS genetic subtypes are reported by van Bosse and Butler [65]. Reduced morbidities are also recognized with improved function in children with PWS treated by GH suggesting that any potential risks of such treatment are favorably balanced by its benefits [74, 75, 145].

Early studies with growth hormone replacement in PWS children provided strong evidence that growth velocity was substantially improved. Treatment with growth hormone doses of 0.125 mg/kg/week showed an increased growth rate of 130%, 300%, and 600% of baseline in three of four treated children with PWS [146]. This study allowed for larger and more rigorous investigations of PWS subjects, which further delineated the presence of growth hormone insufficiency in children with PWS and provided convincing evidence that growth hormone replacement not only increases stature but also improves lean muscle mass, decreases body fat, increases exercise capacity and physical activity,

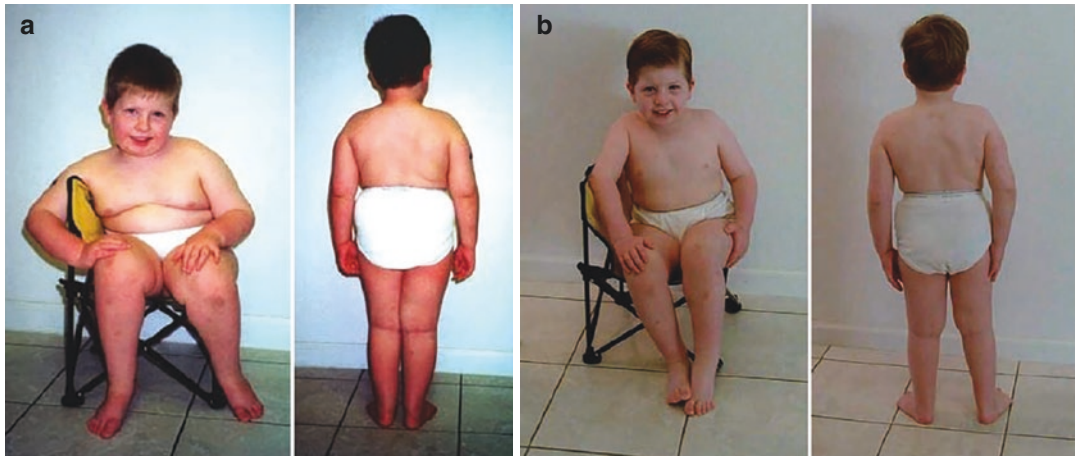

Fig. 1.8 Five-year-old boy with Prader-Willi syndrome before (**a**) and after 3 months of growth hormone (GH) treatment (**b**). Note the improved body habitus, muscle bulk, and reduced fat. The patient was able to increase total caloric intake, and he had increased activity and wakefulness. (Reprinted with permission from Cassidy [199]. Copyright©2000 by Lippincott Williams & Wilkins)

and improves respiratory function. For example, a 25% reduction in total body fat was achieved with a corresponding 30% increase in fat-free mass, measurable by DXA and bioelectrical impedance, in children with PWS [142]. In addition, some parents reported improved behavior in their child with PWS undergoing growth hormone therapy, although additional long-term studies are needed. The positive changes in body composition (Fig. 1.8) appear to be due to growth hormone treatment and not due to changes in caloric intake or exercise regime. Potential side effects have been recognized, including the risk for type 2 diabetes mellitus and worsening of scoliosis in PWS subjects. Growth hormone appears to have a high level of safety in the child with PWS and holds promise for potential benefits in adults with the syndrome not previously treated with growth hormone, although there is a paucity of data in adults. Additional information regarding use, benefits, and potential side effects of growth hormone treatment will be described in more detail elsewhere.

Many clinical features in PWS support growth hormone deficiency, which has been documented by a low peak growth hormone response to provocative stimulation tests, decreased random growth hormone secretion, and low serum insulin-like growth factor I (IGF-I) levels in several studies in over 300 affected children [147]. Additionally, 40–100% of children with PWS have fulfilled the criteria for growth hormone deficiency, which is may often, defined as a peak growth hormone level of less than 10 μg/l in response to one or two stimulation tests. Along with insufficient growth hormone secretion, PWS subjects have a dysfunctional hypothalamic-pituitary-gonadal axis, which may contribute to thermoinstability and a high pain threshold and appears to play a role in the abnormal appetite and incomplete sexual development. This axis and disturbances seen in PWS will be discussed in more detail elsewhere.

Routine Blood Studies

Both normal and elevated levels of cholesterol and lipids have been reported in subjects with PWS [112, 114, 116, 148]. Amino acid levels are reported to be normal in PWS subjects [113]. For example, Butler et al. [114] reported a comparison study of plasma lipid, cholesterol, glucose, and insulin levels in 26 subjects with Prader-Willi syndrome (deletion and nondeletion) and 32 individuals with simple obesity. The average percentage of ideal body weight (IBW) for the reported PWS group was 175.6 ± 68.0 compared with

150.3 ± 43.8 for the obese subjects. Fasting plasma lipid, glucose, and insulin levels were not significantly different between the two subject groups, but insulin levels were higher than the normative nonobese ranges. However, no significant correlations in lipid levels were found in subjects with PWS (deletion or nondeletion) compared with obese individuals for either age or percentage of IBW. No consistent abnormalities were reported in fasting plasma amino acid or urine organic acid levels in PWS subjects compared with obese controls, and similarly for thyroid hormone, spontaneous cortisol, and ACTH levels. Basal prolactin levels were reported within the normal range in PWS subjects. However, plasma gamma-aminobutyric acid (GABA), dehydroepiandrosterone (DHEA), and DHEA-sulfate levels were reportedly elevated in PWS subjects [101, 147].

Butler et al. [149] reported a 6-year-old PWS male with maternal disomy 15 and ethylmalonic aciduria, which raised the question of an inborn error of metabolism, particularly a mitochondrial abnormality. Fasting plasma coenzyme Q10, an oxygen scavenger utilized in the mitochondria or the power plant of the cell for the electron transport chain involved in cellular metabolism and energy expenditure, was measured in PWS subjects and compared with obese and nonobese subjects [150]. No significant differences were found in the coenzyme Q10 levels in PWS subjects compared with similarly aged obese subjects; however, lower coenzyme Q10 levels were found in the PWS subjects compared with nonobese controls. The role of the mitochondria in decreased energy expenditure and the lower metabolic rate in PWS will require further testing.

Brain and Imaging Studies

Although most autopsy studies in PWS subjects have been unremarkable, recent reports have suggested that the paraventricular nucleus (a region of the brain involved in the control of appetite and sexual behavior) may be reduced in size, with fewer oxytocin-expressing neurons. Further studies by Swaab [151] showed a 30% reduction in the growth hormone-releasing hormone (GHRH) neurons in the arcuate nucleus, a key brain region for the release of neuropeptides involved in eating behavior. These changes in the hypothalamic region may be sufficient to impair the regulation of food intake and may be the result of a defective protein (or lack of a protein) due to the chromosome 15 abnormality and interference in gene regulation. This protein derangement may interfere with several systems through gene transcription errors, thereby affecting a regulatory protein impacting on neurotransmitter or neurohormone levels. An example is the *SNRPN* gene, which is expressed in the brain and involved with splicing messenger RNA. This paternally expressed gene is found in the 15q11–q13 region and deleted in the majority of PWS subjects or with lack of expression in those with maternal disomy. This loss may impact on the function of the hypothalamus and lead to altered hypothalamic neuron and neuroendocrine function. The differential expression of a second gene called *7B2* in the hypothalamus of subjects with PWS may also be affected by this genetic derangement [152]. However, the gene expression for ghrelin, peptide YY, and their receptors was studied and found to be present in brain tissue from both PWS and control subjects [92].

The product of gene *7B2* is a neuroendocrine chaperone protein that interacts with prohormone convertase PC2, involved in the regulated secretory pathway in the brain impacting on function. The *7B2* gene is located in the 15q13–q14 region, close to the 15q11–q13 region involved in PWS. Therefore, alteration of the 15q11–q13 region (e.g., deletion) may impact on regulation or activity of the *7B2* gene in PWS subjects, as recently reported. Hence, Gabreels et al. [152] studied the presence of the neuroendocrine 7B2 protein in the supraoptic and paraventricular nucleus of the hypothalamus of five subjects with PWS using antibodies against various segments of the 7B2 precursor polypeptide. Three of the 5 PWS subjects showed no reaction to the 7B2 antibody, MON-12, while 30 control subjects showed a positive reaction. Thus, there was a clear modification of 7B2 expression in some PWS subjects, indicating altered neuroendocrine

function. In a similar report, these authors showed no antibody reaction in these brain nuclei against processed vasopressin, another brain-released hormone, but did show reactivity against the vasopressin precursor [153]. Preliminary molecular genetic data on the *7B2* gene in eight individuals with PWS showed abnormalities (M.G. Butler, "unpublished data"), but additional studies are warranted. In addition, preliminary genome-wide expression using gene microarray technology showed over- and under-expression of dozens of lipid metabolism and neurodevelopmental genes, when comparing brain and somatic tissues of PWS subjects matched with controls [92, 154, 155].

Prader-Willi syndrome is caused by a loss of paternally expressed genes on chromosome 15 with canonical PWS phenotypes including hyperphagic obesity, central hypogonadism, and low growth hormone. Rare PWS microdeletions have defined a 91-kb minimum critical deletion region encompassing three genes, including the noncoding RNA gene SNORD116. Studies have shown that protein and transcript levels of the nescient helix-loop-helix 2 (NHLH2) gene and the prohormone convertase PC1 (encoded by PCSK1 gene) were reduced in PWS patient-induced pluripotent stem cell-derived (iPSC-derived) neurons. Both Nhlh2 and Pcsk1 expressions were reduced in hypothalami of fasted Snord116 paternal knockout (Snord116p−/m+) mice exhibiting relative hyperphagia. Mice with Nhlh2 deficiency display growth deficiencies during adolescence and hypogonadism, hyperphagia, and obesity as adults as it promotes Pcsk1 expression. Humans deficient in PC1 also display hyperphagia, obesity, hypogonadism along with decreased GH levels and hypoinsulinemic diabetes related to impaired prohormone processing. Hence, evidence supports deficits in prohormone processing of proinsulin, pro-GH-releasing hormone, and pro-ghrelin, thereby possibly contributing to neuroendocrine features seen in PWS due to PC1 deficiency, and requires more studies [156].

Positron emission tomography (PET) scans and magnetic resonance imaging (MRI) studies in PWS have revealed disturbances in the hypothalamic region of the brain, suggesting possible dysfunction. Additionally, abnormal cortical development was reported using 3D MRI in PWS subjects [91]. Specialized proton magnetic resonance spectroscopy (MRS) of the brain in subjects with PWS and MRI images revealed mild abnormalities including slight ventriculomegaly, cortical atrophy, and a small brain stem. Other methods to examine brain chemistry and metabolites include N-acetylaspartate choline (NAA/Cho) and N-acetylaspartate/creatine (NAA/Cr) ratios, which were decreased in subjects with PWS, although the Cho/Cr ratio did not differ from control subjects. Thus, neuron loss or dysfunction was suggested in PWS [157]. Parietal lobe pathology detected on 1H magnetic resonance spectroscopy may also be associated with more global brain damage and loss of cognitive function.

Neuroimaging studies undertaken in obese children with and without PWS have shown significant differences in brain activation patterns and structure. For example, Xu et al. [158] used T1-weighted and diffusion tensor magnetic resonance imaging in children with obesity with and without PWS and healthy controls and found both PWS and obese children without PWS exhibited alterations in cortical volume. Similar deficit patterns were seen in ten covarying brain regions including the bilateral dorsolateral and medial prefrontal cortices, right anterior cingulate cortex, and bilateral temporal lobe. Using probabilistic tractography, the PWS group exhibited distinct changes in reduced fractional anisotropy of white matter fibers connected to the covarying regions. The obese children without PWS did not show these findings. They concluded that PWS and obese children share similar gray matter alterations responsible for development of eating disorders and might explain the excessive food intake and constant hunger seen in both groups of children.

Although PWS is the most common genetic syndrome with marked obesity associated with learning, behavioral, and psychiatric problems with neuroendocrine deficits, a longer life expectancy is anticipated due to an earlier diagnosis and treatment. With longer life expectancy, con-

cerns about alterations in brain structure and function associated with advanced age becomes more apparent. In addition, altered gene expression in PWS, metabolic complications and hormonal deficits, might cause earlier onset of physiological and brain aging. To predict brain age, gray and white matter maps were derived from structural neuroimaging data using T1-weighted magnetic resonance imaging (MRI) scans from PWS subjects. Brain-predicted age difference (brain-PAD) scores were calculated based on differences between chronological age and brain-predicted age. This study by Azor et al. [159] designed a method to reflect deviations from healthy brain aging, with higher brain-PAD scores indicating premature aging. Two separate adult cohorts (PWS and controls) underwent brain-predicted age calculation. In the PWS group, brain-PAD scores were not associated with IQ, use of hormonal and psychotropic medications, nor severity of repetitive or disruptive behaviors. However, their data indicated abnormal brain structure in PWS that may reflect premature brain aging or abnormal brain development. Additional longitudinal neuroimaging studies are needed including associations with PWS genetic subtypes and relationship with obesity and family history of dementia [159].

Much of obesity research is focused on the clinical features including adiposity measures and eating behavior or peripheral appetite-regulatory peptides (leptin, ghrelin); advances in neuroimaging studies such functional MRI have demonstrated reward circuitry regions associated with appetite-regulatory hormones involved in development and maintenance of obesity. PWS is a major obesity disorder with known multisystem dysfunction of the inhibitory and satiety mechanisms. Holsen et al. [160] investigated subcortical food motivation circuitry and prefrontal inhibitory circuitry in PWS in response to food stimuli before and after consuming a meal in comparison with obese and nonobese healthy subjects. They viewed food and nonfood images while undergoing functional MRI testing before and after eating while examining the hypothalamus, nucleus accumbens (NAc), amygdala, hippocampus, OFC, and medial PFC and DLPFC. Compared with obese and nonobese healthy individuals, PWS males and females demonstrated higher activity in reward/limbic regions (NAc, amygdala) and lower activity in the hypothalamus and hippocampus in response to food (vs nonfood) images during pre-meal sessions. PWS subjects exhibited higher subcortical activation (hypothalamus, amygdala, hippocampus) when compared with obese and nonobese healthy subjects following a meal. Those with obesity without PWS or nonobese healthy weight controls showed significantly higher activity levels in cortical regions (DLPFC, OFC) associated with inhibitory control. PWS subjects appeared to have results suggesting hyperactivity in the subcortical reward circuitry and hypoactivity in cortical inhibitory regions after eating compared with obese subjects. These observations provide further evidence of neural substrate disturbances associated with variable abnormal food motivation phenotypes in PWS than in simple obesity.

PWS is a neurodevelopmental genetic disorder with obesity, and individuals have an insatiable appetite with compulsive eating leading to detrimental health consequences. To target a therapeutic approach, transcranial direct current stimulation (tDCS) was applied to modulate decision-making and cue-induced food craving in adults; Bravo et al. [46] conducted a multicenter double-blind study of tDCS modulation of food drive and craving in adult participants with PWS, obesity, and healthy weight controls. PWS and obese subjects received five consecutive daily sessions of active or sham tDCS over the right dorsolateral prefrontal cortex (DLPFC), while healthy controls received a single sham and active tDCS in a crossover design. Standardized psychometric instruments assessed food craving, drive, and hyperphagia by self-report and caregiver assessment over 30 days. Robust baseline differences were observed in severity scores for the Three-Factor Eating Questionnaire (TFE) and the Dykens Hyperphagia Questionnaire (DHQ) for PWS compared to healthy weight controls, while obese adults were more similar to healthy weight controls. Active tDCS stimulation in PWS was associated with a significant change from baseline in TFEQ disinhibition (Factor II) at

30 days and total scores at 30 days along with participant ratings of the DHQ severity at 5 days and total scores at 15 days. Sustained neuromodulatory effects and efficacy of tDCS was found with a reduction in food drive and behaviors impacting hyperphagia in PWS and may represent a low-risk and low-cost method to improve care, management, and quality of life in PWS [46].

Cognitive and Behavioral Findings

Decreased intellectual functioning was among the four original defining characteristics of PWS [10, 161, 162]. IQs have ranged from 12 to 100 in previous studies in PWS [13, 115, 162–167], but the average IQ is typically in the mild range of intellectual disability (IQ of 55–70). The distribution includes a few reports within the 85–100 IQ range and other reports within the profound-to-severe range of intellectual disability (IQ < 40). Greenswag [75] reported the IQ in a large survey of PWS subjects and found that IQ was greater than 85 in about 5% of subjects, about 25% had borderline intellectual disability, 35% had mild intellectual disability, 25% had moderate intellectual disability, and about 5% had severe intellectual disability.

Although approximately 30% of PWS individuals have IQs in the normal or borderline range, cognitive dysfunction is nearly always present. However, body weight may correlate with IQ in PWS individuals. For example, Crnic and colleagues [163] reported that individuals with PWS who were never obese had significantly higher IQ scores (mean = 80.2) than PWS subjects who were currently obese (mean = 57.3) or had been obese and lost weight (mean = 59.9).

Interestingly, individuals with PWS may have greater-than-expected abilities to recognize and evaluate figures and shapes and strengths in tasks requiring integration of stimuli in a spatial relationship. The reports of superior puzzle-solving ability in PWS individuals would be consistent with this observation [85, 168]. Dykens [168] studied children with PWS in order to characterize their presumed ability at jigsaw puzzles. She reported relative strengths on standardized visual-spatial tasks such as object assembly, and the scores were significantly higher in PWS subjects compared with age- and IQ-matched control subjects with mixed intellectual disability, but below those of age-matched normal children with average IQs. In contrast, children with Prader-Willi syndrome scored similarly to normal peers on word searches and outperformed them on jigsaw puzzles, placing more than twice as many pieces as the typically developing group.

Warren and Hunt [164] found that children with PWS performed less well on a picture recognition task than children with intellectual disability of unknown etiology matched for chronological age and IQ. The two groups of children performed similarly on a task meant to measure access to long-term memory. There are few studies on learning and memory in PWS, although it is thought that children with PWS have a deficit in short-term visual memory but not in long-term visual storage [164]. As mentioned earlier, visual perception, organization, and puzzle-solving skills are reported as relative strengths in some people with PWS, including stronger visual memory in the PWS subjects with maternal disomy compared with those with typical deletions [169].

Early studies have reported that reading abilities may be better than arithmetic abilities in most PWS subjects, although both are deficient [166]. Greenswag [35] reported that 75% of 232 PWS individuals analyzed had received special education services and typically performed at the sixth grade or lower level in reading and at the third grade or lower in mathematics. Reading problems in PWS may be exacerbated by visual perceptual deficits, particularly in the maternal disomy subjects. While PWS individuals with typical deletions may often, have a lower verbal IQ, those with maternal disomy exhibit a deficit in visual processing on some tasks, which may offset their greater verbal ability. However, Dykens et al. [166] reported that adolescents and adults with PWS have overall standard academic achievement scores higher than their ability measures. Multiple articulation errors (dysarthria), reduced intelligibility, and delayed language

skills (vocabulary, syntax, and morphologic abilities) in children with PWS have been noted.

Dykens et al. [166] reported that daily living skills may change with increasing age in PWS. Thompson and Butler (unpublished data) found that PWS subjects and IQ-matched controls differed substantially in their degree of independent community living skills. The PWS subjects appeared significantly less competent than controls. While this may indicate biologically based differences in cognitive ability, it may also reflect the far more restricted lives that most individuals with PWS lead (and therefore more limited opportunities to develop skills) due to the concerns that caregivers have about access to food in uncontrolled settings.

Butler et al. [1, 165] collected clinical, genetic, cognitive, academic, and behavioral data from 49 individuals with PWS (22 males, 27 females; 27 with the typical 15q deletion, 21 with maternal disomy 15, and 1 with an imprinting defect), ranging in age from 10 to 50 years, and 27 control participants. We found that PWS participants obtained significantly worse, than control subjects in performance IQ ($p < 0.05$), visual-motor skills ($p < 0.01$), and adaptive functioning as assessed by the broad independence ($p < 0.01$), community independence ($p < 0.01$), and motor skill ($p < 0.001$) dimensions of the Scales of Independent Behavior. No significant differences were found for measures of academic achievement. With respect to maladaptive behaviors, PWS participants demonstrated significantly higher levels of self-injury on the Reiss ($p < 0.05$) and higher scores on the general maladaptive index ($p < 0.05$) of the Scales of Independent Behavior, indicating worse behavior.

To further assess cognitive and neurobehavioral aspects in PWS, advanced genetic testing using high-resolution microarrays, chromosome 15 genotyping, and MS-MLPA assays were undertaken on 72 adult residents living in a specialty PWS group home system and clinical psychiatric evaluations performed with Diagnostic and Statistical Manual (DSM)-IV-TR criteria to establish neuropsychiatric aspects in PWS adults and correlation with PWS genetic subtypes [170]. Seventy of the 72 residents were genetically confirmed, and 51% had the larger typical Type I or smaller Type II deletion; 42% had UPD15, and 7% were reported with imprinting defects identified from three separate families. Psychiatric comorbidities included anxiety disorder (38%), excoriation (skin picking) (33%), intermittent explosive disorder (30% but at a threefold increase in males) and psychotic features (23%). Psychiatric diagnoses were no different between UPD15 vs deletion, but more diagnoses were found in those with the larger Type I (4.3) vs the smaller Type II (3.6) deletion when age was adjusted. Adults with PWS presented with uniformly higher rates of psychiatric comorbidities which differed by genetic subtype with gender-specific trends [170]. In a separate study, significantly higher IQ scores were found in a pediatric PWS cohort treated with growth hormone (GH) that particularly involved vocabulary IQ when compared with those not treated with GH. In the same report but with an adult-based nongrowth hormone-treated PWS cohort, those with the 15q11–q13 deletion had lower verbal IQ scores compared with those with UPD15, but difference was seen in body mass index based on the PWS molecular class. Hence, in this study, growth hormone may influence intelligence and may be further impacted by the PWS genetic subtype and possibly age [145].

Behavioral Issues

Several behavioral and psychological findings can be present in individuals with PWS including temper tantrums, stubbornness, hoarding, manipulative behavior, depression, emotional lability, arguing, worrying, compulsive behavior, skin picking, difficulty adapting to new situations, difficulty relating to peers, poor social relationships, low self-esteem, and difficulty in detecting social cues from other people [35, 51, 85, 115, 165–167]. Individuals with PWS are may often, more verbally aggressive and self-assaultive but less sexually inappropriate, than study controls. Children with PWS may be immature and clumsy and more likely to be disliked and teased by their peers. However, they also can be caring and

affectionate. Not all individuals with PWS will have the behavior problems that have been reported. A further description and discussion of the behavioral characteristics will be presented elsewhere, but comparison of PWS and autism have been made as PWS is associated with a distinct behavioral phenotype that in some respects overlaps with autism spectrum disorders (ASD). ASD is a neurodevelopmental disorder characterized by restrictive or repetitive behaviors (RRBs) and social-communication impairment. Thompson, Butler, and others reviewed published literature investigating core ASD symptoms in PWS and provided a prevalence estimate of ASD in PWS [40, 165, 167]. Two independent reviewers searched Medline, CINAHL, PsychINFO, Embase, and Web of Science to find studies that answered the research questions. Individuals with PWS demonstrate significant levels of RRBs and social-communication impairment, in some reports reaching similar levels to those of non-PWS ASD comparison groups. Individuals with UPD had more social-communication impairment than those with DEL. Of 786 PWS participants, 210 (26.7%) were reported as meeting criteria for ASD, either based on clinical diagnosis or by exceeding clinical cut points on relevant ASD symptom measures. In studies that distinguished genetic subtypes, rates of ASD were higher in individuals with PWS with UPD (67 of 190; 35.3%) than those with DEL (47 of 254; 18.5%).

Self-Injurious Behavior

Skin picking and other forms of self-abusive behavior are found at some time in most persons with this syndrome and also can be seen in individuals with autism and other related developmental disorders (e.g., Retrepo et al. [171]). Infections in the involved skin areas can occur. Occasionally, an area may be picked for several years. Serious health problems from persistent self-injury may occur and include eye poking, subdural hemorrhage from forceful head banging, infections from self-inflicted skin picking, and anorectal disease from rectal picking and digging [172]. Studies may reveal one or more ulcers in the rectum, which can be confused with inflammatory bowel disease.

Self-injurious behaviors can be among the most clinically problematic behaviors associated with Prader-Willi syndrome. Previous studies have found self-injurious behavior (most notably skin picking) to be a prevalent behavioral problem in 69% of adolescents with Prader-Willi syndrome [173] and in 81% of adults [174]. Symons et al. [175] surveyed families of 62 persons (24 males, 38 females; mean age of 18 years; age range 3–44 years) with Prader-Willi syndrome and determined the prevalence, topographies, and specific body locations of self-injurious behavior. Self-injury was reported for 81% of the participants, with over 800 self-injury body sites recorded. Skin picking was the most prevalent form of self-injury (82%), followed by nose picking (28%), hand biting (17%), head banging (14%), hair pulling (9%), and rectal picking (6%). The front of the legs and head were disproportionately targeted as preferred self-injury body sites.

Among school-age students with intellectual disability, Symons et al. [175] found that the most common forms of self-injury were biting, head banging, and hitting, whereas picking and pinching were more common among the PWS subjects. Non-PWS individuals with intellectual disability tend to direct self-injury toward the head, while PWS subjects tend to distribute self-injury widely across the body including specific finger, arm, and leg areas. Other forms of self-abusive behavior have been reported, including trichotillomania, rectal picking, pushing pins and tacks into skin, and pulling out nails [172]. Onset of these behaviors is variable, may often, during childhood, but sometimes not until adolescence or early adulthood.

The etiology and pathophysiological mechanisms of self-injury are poorly understood. The primary pharmacological approaches for treating self-injury in persons with intellectual disability and related developmental disabilities are aimed at the dopaminergic system (i.e., neuroleptics), the serotonergic systems (i.e., serotonin reuptake inhibitors), or the endogenous opioid peptide

systems (i.e., opiate antagonists) [102, 176]. Some pharmacological approaches to treating self-injury among persons with Prader-Willi syndrome have been useful [177, 178].

Compulsive Behavior

Dykens et al. [37] reported that compulsive symptoms are found in up to 60% of persons studied with PWS. Obsessive-compulsive disorder (OCD) [13, 35] symptoms may often, begin in adolescence or adulthood in the non-PWS population, and the compulsive behaviors are believed to reduce or prevent anxiety. A large body of evidence has implicated serotonergic mechanisms as underlying the clinical manifestations of OCD in other neuropsychiatric populations [179]. Pharmacologic agents that inhibit serotonin reuptake (e.g., clomipramine) have produced clinical improvements as well as changes in peripheral measures of serotonin function [32, 180], and the use of these agents has improved compulsivity and reduced OCD symptoms in some individuals with PWS [181, 182]. Similarities in the number, type, and severity of compulsive behaviors in adults with PWS and those with OCD have been reported [165, 183]. However, compulsive behavior in typically developing children decreases from 2 to 6 years, while compulsivity increases in children with PWS during this age range [184, 185]. There appears to be a temporal correlation between appetite onset and compulsivity and tantrums in children with PWS. While people with PWS have compulsive disorder that overlaps with that seen in other conditions (e.g., OCD, autism), it may also involve different mechanisms.

On the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Butler, Thompson, and colleagues [39, 167] found group differences between PWS and control participants for the total ($p < 0.05$) and compulsions ($p < 0.01$) scores, as well as for specific aspects of severity of compulsions: time spent performing compulsions ($p < 0.01$), length of compulsion-free intervals ($p < 0.01$), interference with daily activities ($p < 0.01$), and degree of control over compulsions ($p < 0.01$). In contrast, significant group differences were not obtained for any Yale-Brown Obsessive Compulsive Scale obsession scores, or for internal aspects of compulsive behaviors, such as the individual's effort to resist against compulsions. To further characterize and rate the level of hyperphagia and food-seeking behavior seen in PWS, a 13-item questionnaire form was developed by examining developmental and psychological correlates of hyperphagia in PWS. Factor analyses identified three groupings which accounted for 59% of the variance: hyperphagic behaviors, drive, and severity. Hyperphagic behavior appeared to increase with age, while drive appeared to remain stable. The last category (severity) was lower in older adults. Hyperphagic drive and severity were positively correlated with nonfood behavior problems. This questionnaire form is now used in an abbreviated version to assess hyperphagia in clinical trials in PWS [186].

It appears that people with PWS have a compulsive-related disorder, but probably not identical to compulsive disorder seen in other conditions such as autism, Tourette's syndrome, and obsessive-compulsive disorder alone. We further speculate that the lack of GABA-ergic inhibition of dopaminergic and serotonergic neurons in the orbitofrontal and prefrontal cortex and head of the caudate nucleus may be implicated in the compulsive symptoms seen due to the following: the presence of three GABA-A receptor genes (alpha 5, beta 3, gamma 3) in the chromosome 15q11–q13 region; our findings of elevated levels of GABA in plasma of individuals with PWS and Angelman syndrome (as previously indicated, possibly reflecting upregulation of GABA due to improper binding at GABA receptors); and recent gene expression studies with paternal bias of the GABA receptor genes [154, 155]. There are reports that psychotropic medications reduce obsessive-compulsive disorder symptoms in other people and tend to reduce tantrums and compulsive behavior in people with PWS [177, 178, 181], but this area has been poorly studied in PWS with pharmacogenetic testing and impact on medication metabolism.

Genetic Subtype-Phenotype Relationships

Clinical, Behavior, and Cognition

Phenotypic clinical differences among individuals with Prader-Willi syndrome having separate genetic subtypes (typical deletion, maternal disomy, or imprinting defect) are important to study to learn about the role of specific genes and their clinical outcomes. The correlation of specific clinical manifestations and genetic findings will enhance our understanding of genomic imprinting and genotype/phenotype correlations in PWS. The rarity of individuals with imprinting defects has limited their comparison to those individuals with typical deletions or maternal disomy for genetic and clinical correlation studies. The phenotypic spectrum of PWS is quite variable and may be dependent on the genetic subtype. In addition, genotype/phenotype differences may be helpful in guiding the clinician in the evaluation of patients with suspected PWS and in providing prognostic counseling for families once the diagnosis (and specific genetic subtype) of PWS is established.

Hypopigmentation (i.e., lighter hair, eye, and skin colors compared with other family members at a similar age) has been noted to occur at a higher frequency in PWS subjects with the typical chromosome 15 deletion [2, 13, 15] and is found to be associated with a deletion of the *P* gene, which is involved in pigment production, localized at the distal end of the chromosome 15q11–q13 region. Molecular genetic studies have shown that hypopigmentation does not correlate with the DNA haplotype pattern in the region of the *P* gene [187]. In addition, the *P* gene is not considered to be imprinted and is expressed in both chromosome 15s but deleted from one member of the pair in PWS (and AS) subjects with the typical 15q11–q13 chromosome deletion, leading to a decreased amount of pigment [154, 155].

Previous studies have revealed that individuals with PWS with the chromosome 15 deletion were more homogeneous than other PWS subjects in their clinical presentation and anthropometric or physical measurements (e.g., radiographic measurements of the bones of the hand), as reflected in the metacarpophalangeal pattern profile. Those with the 15q deletion (males and females) also were more homogeneous than nondeletion subjects with respect to dermatoglyphic plantar findings of the foot, with a lack of plantar interdigital II–IV patterns with almost exclusively hallucal distal loops [188]. Early studies were conducted before the recognition of maternal disomy 15 as the most common cause of the nondeletion status among people with PWS.

With the advent of molecular testing for all subjects with PWS, several studies have been reported to compare the major genetic subtypes (deletion and maternal disomy) with clinical findings. For example, Gillessen-Kaesbach et al. [189] noted lower birth weights in individuals with PWS and the typical deletion subtype, while an increased maternal age was found in the case of those with maternal disomy. This latter observation was consistent with the source of the extra chromosome 15 from the mother during egg production causing trisomy 15, or three chromosome 15s in the fetus, followed by loss of the chromosome 15 donated from the father during early pregnancy, leading to maternal disomy 15 in the fetus at birth. Mitchell et al. [190] also reported a shorter birth length in PWS males with maternal disomy, compared with males having the 15q deletion, and a shorter course of gavage feeding with a later onset of hyperphagia in PWS females with maternal disomy. In addition, Cassidy et al. [191] observed that people with PWS and maternal disomy were less likely to have the typical facial appearance and less likely to show certain behavioral features of PWS, including skin picking, skill with jigsaw puzzles, a high pain threshold, and articulation problems. No significant differences were found between the groups (deletion and maternal disomy) in most other clinical findings including neonatal hypotonia, need for gavage feeding, cryptorchidism, genital hypoplasia, small hands and feet, scoliosis, dental anomalies, sticky saliva, behavioral disturbances, hyperphagia, decreased vomiting, or sleep disorder. Gunay-Aygun et al. [192] reported that the

diagnosis of PWS among individuals with maternal disomy was typically reported later than among those with a deletion, possibly due to a milder phenotype in maternal disomy subjects.

People with PWS may hoard and arrange items excessively. Dykens et al. [36] described differences between the genetic subtypes in PWS subjects such that the deletion group had scores using the Child Behavior Checklist, indicating more compulsive symptoms and more symptom-related distress. In addition, Symons et al. characterized the self-injurious behavior in 62 PWS subjects via a questionnaire survey [175]. PWS individuals with the typical 15q11–q13 deletion injured at significantly more body sites than did individuals with maternal disomy 15. Skin picking was the most common form of self-injury. Thompson and Butler [165] found that PWS subjects with typical deletions exhibited significantly greater self-injury than both a control group and a maternal disomy subgroup. The typical deletion subgroup also displayed scores indicating more compulsivity than the control group and spent more time engaging in compulsive behavior. Their compulsive rituals interfered with their daily living, and they were less able to control their compulsive behavior. Both PWS genetic subgroups showed significantly greater global severity of compulsive behaviors than the control group, while the typical deletion group consistently showed the most severe symptoms of OCD. Subjects with maternal disomy showed an intermediate level of OCD symptoms. Additional studies will be needed to confirm this observation. In addition, Vogels et al. [67] recently reported that psychoses in Prader-Willi syndrome subjects occur more often in those adults with maternal disomy 15 compared with those with the deletion.

Subgroup comparisons in a study by Roof et al. [193] revealed additional differences between PWS deletion and maternal disomy participants in measures of intelligence and academic achievement administered to 38 individuals with PWS (16 males and 22 females; 24 with deletion and 14 with maternal disomy). PWS subjects with maternal disomy 15 had significantly higher verbal IQ scores than those with the deletion ($p < 0.01$). The magnitude of difference in verbal IQ was 9.1 points (69.9 vs 60.8 for maternal disomy and deletion PWS subjects, respectively). Only 17% of the subjects with the 15q11–q13 deletion had a verbal IQ $\geq$ 70, whereas 50% of those with maternal disomy had a verbal IQ $\geq$ 70. However, performance IQ scores did not differ between the two PWS genetic subtype groups (62.2 vs 64.7 for maternal disomy and deletion PWS subjects, respectively). The full-scale IQ did not differ significantly between the two groups (64.1 vs 61.0 for maternal disomy and deletion, respectively). Specific subtest differences were noted in numeric calculation skill, attention, word meanings, factual knowledge, and social reasoning, with the maternal disomy PWS subgroup scoring higher than the typical deletion subgroup. Deletion PWS subgroup subjects scored higher than the maternal disomy subgroup on the object assembly subtest, which further supports specific visual-perceptual skills being a relative strength for the deletion subgroup. This may explain anecdotal accounts of subjects with PWS having an uncanny ability to assemble jigsaw puzzles, and the puzzle proficiency was not predicted by age, IQ, gender, degree of obesity, or obsessive-compulsive symptoms but by the genetic status (specifically higher in the deletion subgroup) [168].

The mechanisms whereby certain skills appear to be preserved in the maternal disomy subgroup have yet to be identified. Whether this phenomenon is caused by genomic imprinting versus the non-imprinting status of genes in the 15q11–q13 region is not known. The presence of more active or expressed genes in maternal disomy individuals may be due to possible dosage mechanisms. If only one allele, or member of a gene pair, is normally expressed (i.e., one allele is active on the mother's chromosome 15 but inactive on the father's chromosome 15), and there are two active copies instead of one copy (e.g., maternal disomy 15), then more gene product is produced, which may be advantageous. Evidence to date further documents the difference between verbal and performance IQ score patterns among subjects with PWS and the deletion versus the maternal disomy subtype.

Visual Perception and Visual Memory

Discrimination of shape of motion testing was performed by Fox et al. [45], wherein forms were generated by random dot elements that varied in element density and temporal correlation. This testing was done in four participant groups (PWS deletion, PWS maternal disomy, comparison subjects, and normal controls). The procedure uses white dots presenting on a computer monitor that blink on and off randomly. Imbedded within the randomly presented dots is a fixed array of dots with a defined form (e.g., the letter "E"), moving slowly from side to side. The array may vary in element density and degree of correlation of the blinking dots. Performances of normal controls exceeded that of all other groups (78% correct, $p < 0.009$). The typical PWS deletion (66%) and equivalent controls (59%) did not differ significantly. However, performance of the maternal disomy group was significantly worse (38%) than any of the other groups ($p < 0.04$). The inferior performance of the maternal disomy group may be attributed to receiving two active alleles of maternally expressed genes influencing the development of the visual system. Other possibilities include the requirements of paternally expressed genes, residual mosaic trisomy in brain tissue, or complex interactions including specific ratios of differentially spliced gene products. Alternatively, since we know people with PWS have elevated plasma GABA, and it has been shown from other studies that excessive GABA levels have deleterious effects on retinal functioning, it is possible that visual signal strengths could be compromised at the level of initial input, which would manifest itself as a perceptual deficit.

Joseph et al. [169] reported substantial differences in visual-spatial memory among PWS individuals with maternal disomy compared with those with deletions. The rate of short-term memory decay among individuals with maternal disomy was considerably slower than in either PWS individuals with typical deletions or matched controls. The study involved 17 individuals with PWS—7 with deletions, 10 with maternal disomy—and 9 matched controls. Each participant performed a visual recognition task. A series of color digital photographs was presented; most were presented twice, and the remainder appeared only once. Photographs presented twice were separated by 0, 10, 30, 50, or 100 intervening photographs. After viewing each photograph, participants indicated whether or not the photograph had been presented previously. This procedure was conducted twice, the first using photographs of foods and the second time using nonfood items. As the number of intervening photographs increased between the first and second presentations, participants were less likely to remember having seen the photograph previously. Performance by the maternal disomy participants was less affected by increasing the number of intervening photographs relative to the other two groups (deletion and non-PWS controls), suggesting superior visual recognition memory.

Phenotypes Associated with Longer Versus Shorter Typical 15q11–q13 Deletions

The majority of people with PWS have a paternally derived interstitial deletion of the 15q11–q13 chromosome region including about 6 million base pairs of DNA. Two proximal breakpoints (BP1 and BP2) where the typical deletion occurs have been reported in this region. Type I deletions (involving BP1) are larger than Type II deletions (involving BP2) by about 500 kilobases of DNA and includes four additional genes (*NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5*) [194]. Clinical, anthropometric, and behavioral data were analyzed in 12 PWS subjects (5 males, 7 females; mean age 25.9 ± 8.8 years) with Type I deletion and 14 PWS subjects (6 males, 8 females; mean age 19.6 ± 6.5 years) with Type II deletion, determined by the presence or absence of DNA markers between BP1 and BP2 [18]. PWS subjects with the longer typical deletions had test scores indicating more self-injurious and maladaptive behaviors compared with PWS sub-

jects with shorter typical deletions. In addition, obsessive-compulsive behavior was more evident in PWS subjects with longer deletions. It appears that loss of genetic material between breakpoints BP1 and BP2 significantly increases the severity of behavioral and psychological problems in this syndrome. Four genes have been identified and located between BP1 and BP2 [195]. They may play a role in the brain development or function accounting for our observed clinical differences. The 15q11.2 BP1-BP2 deletion (Burnside-Butler) syndrome is now emerging with a neurodevelopmental-autism phenotype [17, 27] identified as one of the most common high-resolution microarray disturbances accounting for 9% of microarray findings in those presenting for genetic services with developmental delays, autism, or neurodevelopmental disorders [16, 17]. One of those genes, *NIPA1*, is expressed in brain tissue and will require further investigation to determine its role in causing specific clinical findings in PWS but when disturbed causes familial ataxia. It and its gene paralogue (*NIPA2*) both code for magnesium or other cation transporters possibly playing a role in brain function. The *CYFIP1* gene encodes a protein engaged with the *FMR1* gene involved with fragile X syndrome and intellectual disability, while *TUBGCP5* has a role in cytoskeleton [17]. Hence, the Burnside-Butler syndrome due to the 15q11.2 BP1-BP2 deletion and PWS are associated with several physical, cognitive, and behavioral characteristics, particularly those with the larger Type I deletion. For many PWS individuals, compulsive behavior is often noted in both food and nonfood situations. To examine for differences across three separate genetic subtypes in PWS (i.e., Type I or Type II deletions, maternal disomy 15), Zarcone et al. [49] reported on 73 subjects with PWS using the Yale-Brown Obsessive Compulsive Scale and the Compulsive Behavior Checklist. Differences were seen in those with Type I deletions as they had more compulsions related to personal cleanliness (i.e., excessive bathing/grooming), and those compulsions were more difficult to interrupt and disrupted social activities more than seen in the other PWS genetic subtypes, while those with the smaller Type II deletion had more compulsions likely related to specific academic areas (i.e., erasing answers and counting objects or numbers) [49].

Conclusions

Prader-Willi syndrome is a prototypic contiguous gene disorder with several genes in the 15q11–q13 region contributing to the phenotype. PWS and Angelman syndrome were the first examples in humans of genomic imprinting, or due to the difference of genetic expression depending on the parent of origin. Significant behavioral differences distinguish the two major genotypes (typical deletion vs maternal disomy). May often, those with typical deletions of the entire region have had the most severe behavioral phenotype with more skin picking, lower verbal IQ, and hypopigmentation. Those with maternal disomy are more impaired on visual perception but have superior visual recognition memory. With typical deletions, there are two subtypes, a longer (Type I) and shorter (Type II) deletion. The phenotypes of individuals with the longer deletion are more severe in general than those with shorter deletions, and the observation of increased severity in those with the larger 15q11–q13 deletion is also seen in Angelman syndrome [196, 197]. Within the 15q11.2 BP1-BP2 region involving the longer and shorter deletion breakpoints are four protein-coding genes expressed in the brain tissue known to play a role in axon formation, neurogenesis, cellular growth, and magnesium transport implicated in behavioral differences in those with PWS having different deletion sizes [18, 49].

Many features in persons with PWS suggest a hypothalamic dysfunction: hyperphagia, sleep disorders, deficient growth hormone secretion, and hypogonadism. In addition, children with damage to the hypothalamus such as following craniopharyngioma brain tumor surgery can show features similar to PWS including an increased appetite, obesity, learning and behavior problems, a decreased growth rate, and endocrine disturbances. This relationship should be further

pursued in brain pathology and neuroanatomical studies including brain imaging (e.g., functional MRI and optical topography).

A multidisciplinary approach is needed to treat individuals with PWS, regardless of the age of the patient. Primary care physicians such as pediatricians, family physicians, or internists should be able to treat most patients with PWS in consultation with a clinical geneticist, endocrinologist, dietitian, and other experts as needed. Additional information about PWS can be obtained by contacting a local genetics center and through the national and local Prader-Willi syndrome associations [30, 33].

Most individuals with this syndrome can be healthy if diagnosed early, and a treatment plan is in place to avoid the complications of uncontrolled obesity. Additional needs depend on the overall health of the child and the age at diagnosis. Exercises to increase coordination, balance, and strength are important but should be kept simple and low in number at the beginning and gradually increase over time. Consultation with the patient's doctor and physical therapist is recommended before undertaking an exercise program at home or in the school setting. A better understanding of energy expenditure and energy balance in PWS is clearly needed.

There are currently no consistent, well-established behavioral or psychological management methods for overcoming all behavioral problems associated with PWS. The greatest success appears to be obtained by capitalizing upon the inherent compulsivity of people with PWS in devising highly predictable daily routines, the use of behavior management reward systems to promote exercise and diet control, and providing choice whenever feasible within the structured daily schedule. Tasks to improve social skills such as taking turns or working together with peers may be useful. These tasks should be incorporated into the classroom setting by working closely with the school educators and administrators.

Selective serotonin reuptake inhibitors may be helpful in reducing tantrums, while atypical neuroleptics that produce minimal weight gain may be of some value in treating aggressive outbursts [198] that may occur in some PWS individuals [30, 32]. Skin picking appears to be regulated by a different neurochemical mechanism than other compulsive symptoms, which may implicate the lack of GABAergic inhibition at the brain level. No systematic trials of GABA agonists have been reported to date. Pharmacological treatments for weight control and behavior problems have met with only modest results. A better understanding of genome-wide microarray expression in brain and peripheral tissues and recognition of disturbed interconnected gene pathways in PWS may lead to additional treatment modalities.

It is often difficult but vital to find appropriate services to meet the needs of the immediate and extended family as well as teachers. Since nearly one-third of the people with PWS have a low normal IQ, they often do not qualify for intellectual disability services yet are poorly served within most psychiatric programs. Many parents and advocacy organizations have developed specialized residential programs for young adults with PWS to meet this need.

With growth hormone treatment, individuals with PWS will gain increased muscle mass and strength, improved respiratory function, decreased fat mass, increased physical activity and energy expenditure, and taller stature. It is important to diagnose early. PWS subjects may have scoliosis, which could be exacerbated by rapid growth in children with or without PWS regardless of growth hormone treatment. Therefore, checking and monitoring for scoliosis should be performed by their physician on a regular basis before and while receiving growth hormone as described by van Bosse and Butler [65]. Growth hormone treatment in non-PWS populations may be associated with an increased risk for slipped capital femoral epiphysis, a condition that is associated with obesity. Growth hormone treatment also may be associated with an increased incidence of pseudotumor cerebri. Thus, careful monitoring for these findings should be routine in following children with PWS.

Obesity is a major health problem in PWS with an increased risk for type 2 diabetes mellitus

in individuals with PWS and other complications related to obesity. Moreover, growth hormone treatment may decrease insulin sensitivity and further increase the risk for noninsulin-dependent diabetes mellitus. Therefore, all children with PWS and obesity should be carefully monitored for glucose intolerance and diabetes mellitus regardless of growth hormone treatment.

It is reasonable to believe that the improvement in body composition noted in children with PWS on growth hormone therapy should lower the risk for comorbid diseases (e.g., diabetes, high blood pressure, cardiovascular disease). A long life span with a better quality of life would be anticipated. There is a high probability that the growth hormone/insulin growth factor axis deficiency seen in children with PWS is also present in adults. Therefore, adults may also benefit from growth hormone therapy, and a growing literature supports treatment in adults. Understanding the genetic cause and pathophysiology of Prader-Willi syndrome should allow for better treatment options for the future and a better quality of life for those affected with this condition.

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2 Molecular Genetic Findings in Prader-Willi Syndrome

Stefan Stamm and Merlin G. Butler

Prader-Willi syndrome (PWS) is caused by the loss of expression from an imprinted region on chromosome 15q11.2-q13.1. Most PWS patients (about 60%) have a deletion in the paternal chromosome. The deletion can occur between two proximal breakpoints (BP1, BP2) and a common distal breakpoint (BP3). There are very rare instances of different distal breakpoints BP4 and BP5. Type I deletions occur between BP1 and BP3, while type II deletions are between BP2 and BP3. About 35% of PWS patients have uniparental maternal disomy 15, and the remaining patients have an imprinting defect, typically a deletion or epimutation in the imprinting center [1, 2]. Deletions between BP1 and BP2 affect only nonimprinted genes but cause Burnside-Butler syndrome, characterized by neurological, cognitive, and behavioral problems [3].

Here, the properties and functions of genes between BP1 and BP5 are reviewed (Fig. 2.1 and Table 2.1). These genes contribute collectively to PWS, suggesting that not a single gene is solely responsible for the syndrome.

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Genetic Imprinting

Genomic imprinting is the epigenetic marking of a gene based on the parental origin that results in monoallelic expression as one of the paternal alleles is transcriptionally silenced. Imprinting generates a parental-specific gene expression in diploid cells. Imprinting originated after evolution from egg-laying to live-born mammals having a placenta and is present in eutherian mammals (e.g., humans and mice) and marsupials (e.g., kangaroo) [4].

Similar to all autosomes, the gene region on chromosome 15 responsible for the Prader-Willi syndrome is present in two alleles: the maternal one derived from the mother and the paternal one derived from the father. However, due to imprinting, at least five gene expression units are expressed only from the paternal allele in the brain and two genes are only expressed from the maternal allele (Fig. 2.1).

There are 165 human genes and 197 mouse genes currently known to be imprinted that represent about 1% of all genes [5]. Imprinted genes are predominantly found in the placenta where they regulate fetal growth via their influence on placental development and function [6, 7]. Recently, imprinted genes have been increasingly recognized to function in the nervous system [8]. Imprinting can be tissue-specific: for example, two genes from the PWS region, PWRN1 and NPAP1, show biallelic expression in testis but

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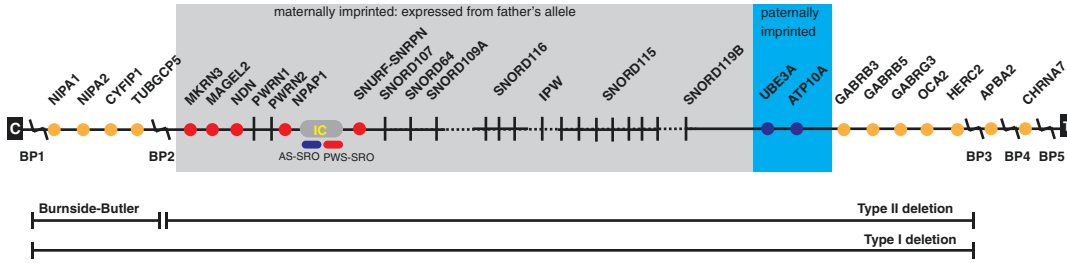

Fig. 2.1 Overview of the genes in the Prader-Willi syndrome region. The genes are abbreviated using the HUGO nomenclature, and the meaning of the abbreviations is explained in Table 2.1. Nonimprinted genes are shown in orange. Maternally imprinted genes are in red, and paternally imprinted genes are in blue. Maternally imprinted genes are expressed from the father's allele, and paternally imprinted genes are expressed from the mother's allele. See the text for tissue or cell-type-specific deviation from these predominant imprints. BP: breakpoints; IC: imprinting center; PWS-SRO: PWS smallest region of overlap; AS: Angelman syndrome smallest region of overlap; C and T: centromere and telomere locations. Lines indicate deletion areas for Burnside-Butler syndrome, type I and type II deletions

Table 2.1 Genes in the PWS region between BP1 and BP5. Imprinted indicates the type of imprint; intron indicates whether an intron is present in the gene

Name	Full name	Imprinted	Intron	Function
Breakpoint 1 (BP1)				
NIPA1	Non-imprinted In Prader-Willi/ Angelman syndrome region protein 1	No	Yes	Magnesium transporter
NIPA2	Nonimprinted In Prader-Willi/ Angelman syndrome region protein 2	No	Yes	Magnesium transporter
CYFIP1	Cytoplasmic FMR1 interacting protein 1 (FMR1: fragile X mental retardation protein)	No	Yes	Regulates protein biosynthesis and actin polymerization, influencing dendritic spines
TUBGCP5	Tubulin gamma complex-associated protein 5	No	Yes	Binds microtubules to the centrosome
Breakpoint 1 (BP2)				
MKRN3	Makorin ring finger protein 3	Maternal	No	E3 ubiquitin ligase, regulates puberty onset
MAGEL2	MAGE family member L2; MAGE: melanoma antigen	Maternal	No	Modulates E3 ubiquitin ligase activity, regulates endosomal sorting
NDN	Neurally differentiated EC cell-derived factor	Maternal	No	Binds to E3 ubiquitin ligase, and E3 SUMO ligase, interacts with hundreds of proteins
PWRN1	Prader-Willi region nonprotein-coding RNA 1	Maternal in brain, biallelic in testes	Yes	Unknown
PWRN2	Prader-Willi region nonprotein coding RNA 2	N/A	Yes	Unknown
NPAP1	Nuclear pore-associated protein 1	Maternal in brain; biallelic in testes	No	Primate-specific part of the nuclear pore complex
SNURF-SNRPN	SNRPN upstream reading frame (*SNURF*) – small nuclear ribonucleoprotein polypeptide N (*SNRPN*) gene	Maternally imprinted	Yes	SNURF: unknown SNRPN: Sm protein, part of U2 and U1 snRNPs in the brain
SNHG14	Small nucleolar RNA host gene 14	Maternally imprinted	Yes	Hosts noncoding RNAs C/D box snoRNAs and ncRNAs (IPW, PWAR)

Table 2.1 (continued)

Name	Full name	Imprinted	Intron	Function
IPW	Imprinted in Prader-Willi	Maternally imprinted	Yes	Regulates gene expression in *DLK1-DIO3* gene region on chromosome 14
UBE3A	E3A ubiquitin-protein ligase	Paternally imprinted	Yes	E3 ubiquitin ligase
ATP10A	ATPase phospholipid transporting 10A protein	Paternally imprinted	Yes	Lipid flippase
GABRB3	GABA A receptor beta3 subunit	No	Yes	Subunit of the gamma amino butyric acid (GABA) receptor
GABRA5	GABA A receptor alpha 5 subunit	No	Yes	Subunit of the gamma amino butyric acid (GABA) receptor
GABRG3	GABA A receptor gamma 3 subunit	No	Yes	Subunit of the gamma amino butyric acid (GABA) receptor
OCA2	Oculocutaneous albinism, type 2	No	Yes	Transmembrane protein regulating pH of melanosomes
HERC2	HECT and RLD domain containing E3 ubiquitin protein ligase 2	No	Yes	E3 ubiquitin ligase
BP3				
APBA2	Amyloid beta A4 precursor protein-binding family A member 2	No	Yes	Regulates generation of β-amyloid
BP4				
CHRNA7	Neuronal acetylcholine receptor subunit alpha-7	No	Yes	Subunit of the acetylcholine receptor

only paternal allele expression in the brain [9, 10]. UBEA3 is generally expressed only from the maternal allele in brain, but data suggest expression from the paternal allele in mouse glial cells [11, 12].

Imprinted genes have general common features. For example, more than 80% of imprinted genes are localized in 16 clusters containing at least two imprinted genes [13], suggesting that imprinting factors regulate multiple genes in *cis* [12, 13]. In general, each cluster contains a DNA sequence that is methylated either in oogenesis (maternal imprint) or spermatogenesis (paternal imprint). With one exception, each cluster expresses a long noncoding RNA (lncRNA) that is typically very large in size, for example, Airn is 108 kb, SNURF-SNRPN is more than 550 kb long [14]. At least two imprinted lncRNAs, SNURF-SNRPN and DLK1-MEG3 [15, 16], host C/D box snoRNAs.

Despite these common structural features, the molecular mechanisms governing imprinting are unclear. DNA methylation is the best understood epigenetic mark that represses transcription when present in promoter regions. The imprint is controlled through an imprinting control region (ICR), also named imprinting center (IC), that retains the methylation on one parental allele. The DNA methylation is caused by DNA methylases (DNMTs) and can be removed in the germline via DNA demethylases. In addition to DNA methylation, histone modifications, such as H3K27me3, can contribute to imprinting [17].

Compared with other known imprinted regions, such as the Igf2r (insulin-like growth factor 2 receptor), Kcnq1 (potassium voltage-gated channel subfamily Q member 1), and Dlk1 (delta-like noncanonical notch ligand 1) clusters, the PWS syndrome region is more complicated due to the large number of genes in the cluster (at least seven) and the mixed paternal imprints: most genes are paternally expressed, but two genes (UE3A and ATP10A) are expressed from the maternal allele. The existence of maternal and paternal imprinted genes in close vicinity also implies the presence of boundary elements containing the imprinting signals that have not yet been identified [14].

Genes in the Maternally Imprinted Region, Not Expressed in PWS

Protein Ubiquitination

Three maternally imprinted proteins (MKRN3, MAGEL2, NECDIN), one paternally imprinted protein (UBE3A), and one nonimprinted protein (HERC2) act in ubiquitin ligation (Fig. 2.2b–f). Ubiquitin is a small protein that is named after its ubiquitous expression, and is found in all eukaryotes. It is attached to numerous proteins, which regulates multiple cellular processes, including protein degradation, protein localization, DNA repair, cell cycle progression, transcription, and cell signaling [18]. Ubiquitination is performed by three subsequent enzymatic steps (Fig. 2.2a): first, E1 ubiquitin-activating enzymes catalyze a thioester bond between E1 and ubiquitin; second, ubiquitin is transferred to E2 ubiquitin-conjugating enzymes; and finally, ubiquitin is transferred from E2 ubiquitin-conjugating enzymes to substrates by E3 ubiquitin ligases. The three different enzymatic steps lead to a cascade of ubiquitination targets as humans express two ubiquitin-activating enzymes that act on at least 35 E2 ubiquitin-conjugating enzymes, which subsequently interact with more than 600

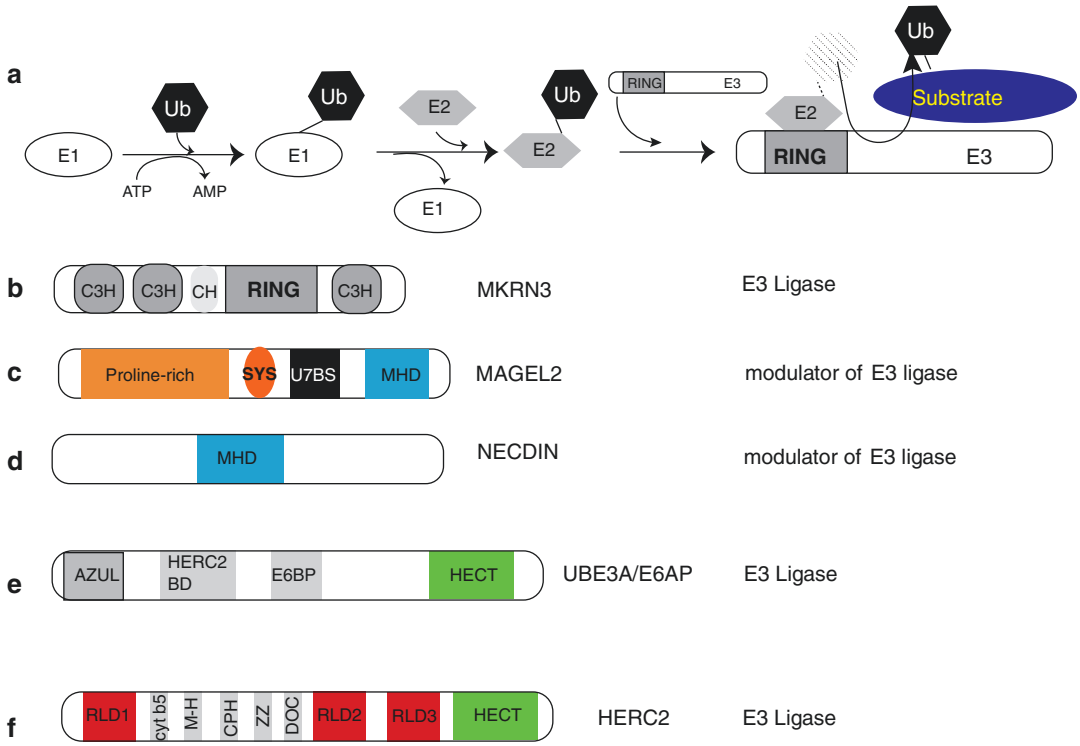

Fig. 2.2 Protein ubiquitination. (**a**) Ubiquitination pathway: E1 ubiquitin-activating enzymes bind ubiquitin while hydrolyzing ATP; ubiquitin is then transferred onto E2 ubiquitin-conjugating enzymes; the E2 ubiquitin-conjugating enzymes bind to E3 ubiquitin ligases that transfer ubiquitin to its final substrate. Ub: ubiquitin; RING: really interesting gene. (**b**) Schematic structure of the MKRN3 protein. C3H: C3H-type ring finger; CH: Macronin-type Cys-His domain, RING domain [23]. (**c**) Schematic structure of the MAGEL2 protein. Proline-rich: proline-rich domain; U7BS: USP7 binding site (ubiquitin-specific peptidase, removes ubiquitin from targets); MHD: MAGE homology domain [171]. SYS is the hotspot for Schaaf-Young syndrome mutations [38]; there are additional SYS mutations in the MHD. (**d**) Schematic structure of NECDIN. MHD: MAGE homology domain [43]. (**e**) Schematic structure of UBE3A. (**f**) Schematic structure of HERC2 [164]

ubiquitin ligases. The most abundant class of ubiquitin ligases contains a RING domain (really interesting new gene) that binds to ubiquitin-loaded E2-conjugating enzyme. RING domains bind zinc, but they can also fold into the same structure without Zn coordination, called the U-box (Fig. 2.2a, b) [19]. MKRN3 is a RING domain E3 ubiquitin ligase; UBE3A and HERC2 are also E3 ubiquitin ligases but contain a HECT domain (homologous to E6-AP C terminus) to perform the catalysis and bind E2 ligases with other protein motifs. E3 ubiquitin ligases can be regulated by proteins binding to their RING domain. For example, MAGEL2 and NECDIN bind to RING domains via their MHD domain (MAGE homology domain).

MKRN3

The MKRN3 gene, initially called ZNF127 [20], is imprinted, and only the paternal allele generates a mRNA and protein. MKRN3 encodes an E3 ubiquitin ligase, which adds ubiquitin moieties onto substrate proteins [21]. MKRN3 stands for Makorin ring finger protein 3. It is part of the Makorin protein family that derives its name from Makor (Hebrew for source) after a novel by Michener [22]. The MKRN3 protein derives from a short pre-mRNA-lacking introns and is thus considered an intronless gene. However, nonprotein-coding isoforms that show intron removal exist. Its 3'UTR overlaps with an antisense RNA. The protein contains four zinc fingers, three of the C3H type and one RING finger in addition to an MKRN3-specific Cys-His domain [23] (Fig. 2.2b).

Mutations in MKRN3 cause central precocious puberty (CPP) [24]. CPP generates puberty before the age of 8 years in girls and 9 years in boys [25] and is caused by the early reactivation of the hypothalamic-pituitary-gonadal axis. Currently, 39 inactivating mutations in the coding sequence of MKRN3 have been described, including 4 nonsense, 13 frameshift, and 22 missense mutations. These mutations are almost all within the zinc finger domains [26].

Due to the imprinting and paternal allele expression, family members inherited their mutations from their fathers [24]. MKRN3 is expressed ubiquitously, but its effect on puberty onset originates from the hypothalamus, especially from the KISS1-positive neurons in the arcuate nucleus and ventromedial nucleus (VMN) of the hypothalamus. MKRN3 suppresses puberty by inhibiting the promoters of KISS1 (KiSS-1 metastasis suppressor) and TAC3 (tachykinin precursor 3), which reduces their transcription. MKRN3 expression drops before the onset of puberty, resulting in an increase of KISS1 and TAC3 expression. This increase of KISS1 and TAC3 results in the secretion of GnRH (gonadotrophin-releasing hormone), which initiates puberty. The inhibiting activity of MKRN3 is dependent on its ubiquitin ligase activity, which explains why MKRN3 mutations located in the RING domain lead to an early onset of puberty as they antagonize MKRN3 activity on KISS1 and TAC3 [21] (Fig. 2.3).

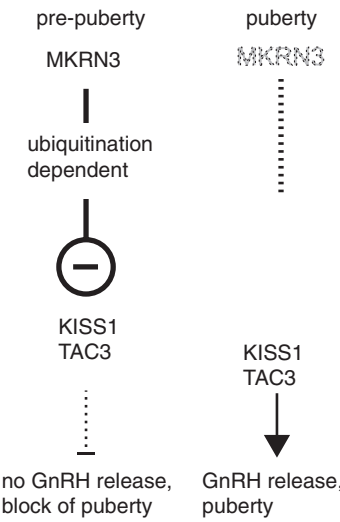

Fig. 2.3 MKRN3 regulates puberty. MKRN3 is expressed in the hypothalamus where it blocks transcription of KISS and TAC3 (tachykinin precursor 3) mRNA via an unknown mechanism that requires MKRN3's ubiquitination activity. At the onset of puberty, MKRN3 mRNA and protein are strongly reduced in the hypothalamus, leading to the transcription of KISS1 and TAC3, which results in the release of GnRH (gonadotrophin-releasing hormone) that initiates puberty

It is not clear whether the loss of MKRN3 in PWS contributes to the disorders of puberty development in PWS [27].

MAGEL2

MAGEL2 is an abbreviation for MAGE family member L2, and MAGE is an acronym for melanoma antigen family. MAGEL2 is imprinted in the brain and is only expressed from the paternal allele. MAGE family members were originally identified as tumor antigens. The MAGE protein family contains 40 members generated through gene duplications in placental animals. Most MAGE genes are located on the X-chromosomes, that is, show monoallelic expression in males and likely females due to X-chromosome inactivation. MAGE genes are localized in clusters, termed MAGE-A, -B, -C, D, E, G, H, and in individual members F1 and L2, as well as the individual member Necdin. In contrast to their ancestral genes in nonplacental species, numerous MAGE genes, including the members of the MAGEA, -B, and -C clusters, MAGEL2, and NECDIN, are intronless [28]. All MAGE proteins contain a MAGE homology (MHD) domain that mediates protein-protein interactions. MAGE proteins can associate with E3 ubiquitin ligases to form MAGE-RING-ligases, which alters the E3 ubiquitin ligase activity, its substrate specificity, and subcellular localization [29, 30] (Figs. 2.2c and 2.4a). Human MAGEL2 can be detected in most tissues, but it is most abundant in the brain, especially in the hypothalamus, nucleus accumbens, and pituitary [31].

MAGEL2 binds to the E3 RING ubiquitin ligase TRIM27. TRIM27 is a member of the

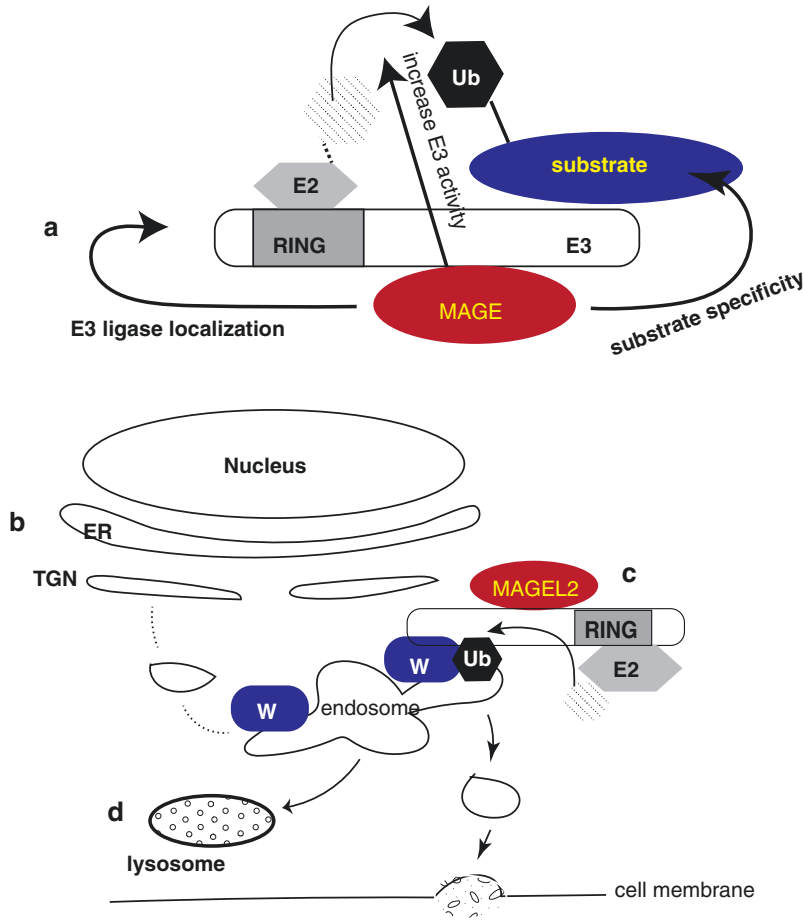

Fig. 2.4 Function of MAGEL2. (**a**) Effect of MAGE proteins on E3 ubiquitin ligases. MAGE protein binds to ubiquitin ligases and can increase their activity or change their substrate specificity and location. (**b**) Membranes from the endoplasmic reticulum (ER) form the trans-Golgi network (TGN) from which endosomes are formed. (**c**) MAGEL2 promotes the ubiquitination of WASHC1 (W) through binding to the E3 ubiquitin ligase TRIM27. Ubiquitination of WASHC1 initiates actin polymerization that sends endosomes to the plasma membrane. (**d**) In the absence of MAGEL2, WASHC1 is not ubiquitinated, resulting in endosomes being sent to lysosomes where their content is degraded

tripartite motif family, characterized by the TRIM motif that contains three domains: a RING domain, B box zinc finger domains, and a coiled-coil region. TRIM27 is found throughout the cell and regulates transcription in the nucleus [32]. MAGEL2 and TRIM27 ubiquitinate WASHC1, which is part of the WASH protein complex that compartmentalizes endosomes by initiating actin polymerization. WASHC1 stands for Wiskott-Aldrich syndrome homolog 1. Endosomes are sorting organelles that transport proteins from the plasma membrane to the trans-Golgi network [33]. Through endosomal compartmentalization, proteins are sorted, i.e. they are either recycled to the plasma membrane or send to lysosomes for degradation. The WASHC1 protein is involved in this sorting process as it recruits a protein complex that initiates actin polymerization [34]. MAGEL2 is recruited to endosomes and promotes ubiquitination of WASHC1 by TRIM27, and this ubiquitination promotes endosomal actin polymerization [35] (Fig. 2.4b–d).

Secretory granules are vesicles generated from the trans-Golgi network that can be rapidly released upon a stimulus [36]. A proteomic study showed that the loss of MAGEL2 found in PWS reduces the amount of secretory granules in human and mouse neurons. This reduction is caused by an increase in lysosomal degradation. The increased lysosomal degradation is likely due to the sorting defect of endosomes, where the endosomal sorting protein WASHC1 is no longer ubiquitinated, resulting in endosomes sent to lysosomes [37]. Through this mechanism, the loss of MAGEL2 could contribute to PWS by reducing neuroendocrine secretion in the hypothalamus.

Nonsense mutations of MAGEL2 result in Schaaf-Yang syndrome (SYS) with 42 of the currently known 78 nonsense mutations clustered in only six nucleotides in the middle of MAGEL2 [38]. This leads to a loss of the MAGE homology domain (MHD). At early ages, Schaaf-Yang syndrome shares several symptoms with PWS, such as developmental delay, neonatal hypotonia, poor suck, and excessive weight gain [38, 39]. However, during adolescence Schaaf-Young syndrome becomes more distinct from PWS.

Necdin/NDN

Necdin (NDN) stands for *n*eurally differentiated *EC* cell-*d*erived factor as it was discovered in a screen of neuronal cell differentiation using retinoic acid on P19 cells [40]. Necdin1 is an intronless gene and is expressed predominantly in the brain where it is imprinted and only expressed from the father's allele. Similar to MAGEL2, necdin is a member of the MAGE protein family and contains a single MAGE domain. It is present both in the cytosol and nucleoplasm, which is determined through its interaction with other proteins. NDN interacts with hundreds of proteins, including Grin1 (glutamate receptor), p75 (neurotrophin receptor), transportin (nuclear import factor), and Htt (huntingtin) in the cytosol and the nucleus with proteins forming complexes with p53 and Crebp (Creb-binding protein) [41]. Functionally, it was shown to bind the ubiquitin E3 ligase Mdm2, leading to degradation of the proapoptotic protein CCAR1/CARP1 (cell cycle apoptosis regulatory protein) [42]. In addition, NDN binds to PIAS1, a RING-type SUMO E3 ligase, via its MHD and regulates PIAS1 activity [43].

Early characterizations showed that Necdin interacts with the transcription factor E2F1 and the p75 neurotrophin receptor that binds NGF, BDNF, NT-3, and NT4/5. Interactions with p75 and E2F1 cause cell cycle arrest. In contrast, the related MAGE family member MAGEL2 does not cause cell cycle arrest [44].

Several knockdown models of Necdin were created that manifest early postnatal lethality with partial penetrance. The mouse models show various phenotypes depending on the genetic background, including respiratory defects, skin scraping, and abnormal neuronal differentiation due to reduced TRKA signaling, differentiation of GABA neurons, and defective axonal outgrowth. Several studies reported hypothalamic changes that showed a reduction of GnRH neurons [45, 46].

PWRN1 and PWRN2

PWRN1 is the abbreviation for Prader-Willi region nonprotein-coding RNA 1. PWRN1 is

most abundantly expressed in testis and is also found in the prostate, heart, kidney, lung, and brain. It shows biallelic expression in testis, but is only paternally expressed in the brain [10]. There is evidence that PWRN1 hosts an alternative promoter of the SNURF-SNRPN gene [47].

PWRN2 is a nonprotein-coding RNA located in an intron of PWRN1 in antisense orientation to PWRN1. The functions of PWRN1 and PWRN2 are not known.

NPAP1/C15orf2

NPAP1 was first named C15orf2 and later renamed NPAP1 for nuclear pore-associated protein 1. It is an intronless gene with the strongest expression in testes, where the expression is biallelic [9]. NPAP1 is imprinted in the brain where it is expressed from the paternal allele and protein can be detected in various brain tissues, including the hypothalamus [48].

The NPAP1 gene shows strong expression of piRNAs [10]. The piRNAs (PiWi-interacting RNAs) are 26–31-long RNAs made from cleaving precursor RNAs and bound to argonaute proteins. They function mainly in the silencing of transposons [49]. Global databases indicate that piRNAs are generated throughout the Prader-Willi region, with NPAP1 forming the most piRNAs of all protein-coding genes [50].

NPAP1 shows sequence similarity with the nuclear pore complex protein POM121 [51]. POM121 is part of the nuclear core complex and has a single-pass transmembrane domain that contributes to anchoring the nuclear pore complex in the nuclear membrane. POM121 enhances the importin-dependent nuclear transport of transcription factors like E2F1 and MYC [52]. NPAP1 colocalizes with the nuclear pore complex inside the nucleus. Overexpression of NPAP1 did not show an effect on transcriptional regulation and global mRNA transport, so the exact molecular function remains unclear [51].

An interesting feature of NPAP1 is that it is primate specific. Paralogs of NPAP1 exist in all placental species, except rodents. Since they are intronless, these paralogs likely derived from an earlier intron-containing POM121 ancestral gene through retrotransposition. This primate specificity is notable as PWS mouse models do not fully recapitulate the human phenotype, most strikingly the obesity [53].

The SNURF-SNRPN Transcriptional Unit

SNURF-SNRPN and Imprinting Center

SNURF-SNRPN stands for SNRPN upstream reading frame (SNURF) – small nuclear ribonucleoprotein polypeptide N (SNRPN) gene (Fig. 2.5a). This gene is imprinted and only expressed from the paternal allele. It is bicistronic, that is, it expresses two proteins, the SNURF and SNRPN protein, from one mRNA (Fig. 2.5b, c). Bicistronic transcripts are common in bacteria, but very rare in eukaryotes. In addition to these two proteins, the gene harbors numerous noncoding RNAs in its 3' UTR, among them at least six classes of C/D box small nucleolar RNAs (snoRNAs) and the IPW (imprinted in Prader-Willi) RNA. The promoter region of the SNURF-SNRPN gene overlaps with the imprinting center, that is, the region that is necessary for methylation of the parental allele.

The imprinting center is defined through microdeletions [54–56] and is responsible for the methylation and silencing of the paternal alleles. The core of the imprinting center is defined by the *s*hortest *r*egion of deletion *o*verlap between PWS patients and a paternal imprinting defect (PWS-SRO). Conversely, the smallest region of deletion overlap between Angelman syndrome patients and a maternal imprinting defect is described as AS-SRO. The PWS-SRO activates the paternal allele and keeps the allele active, whereas the AS-SRO is necessary for the maternal pattern of expression [57]. It is highly unusual that imprinting centers for the maternal and paternal alleles are so close together.

The SNURF-SNRPN gene consists of at least 8 coding exons and at least 11 noncoding upstream exons. There are three major transcriptional start sites in exons 1, U1A, and U1B. Both

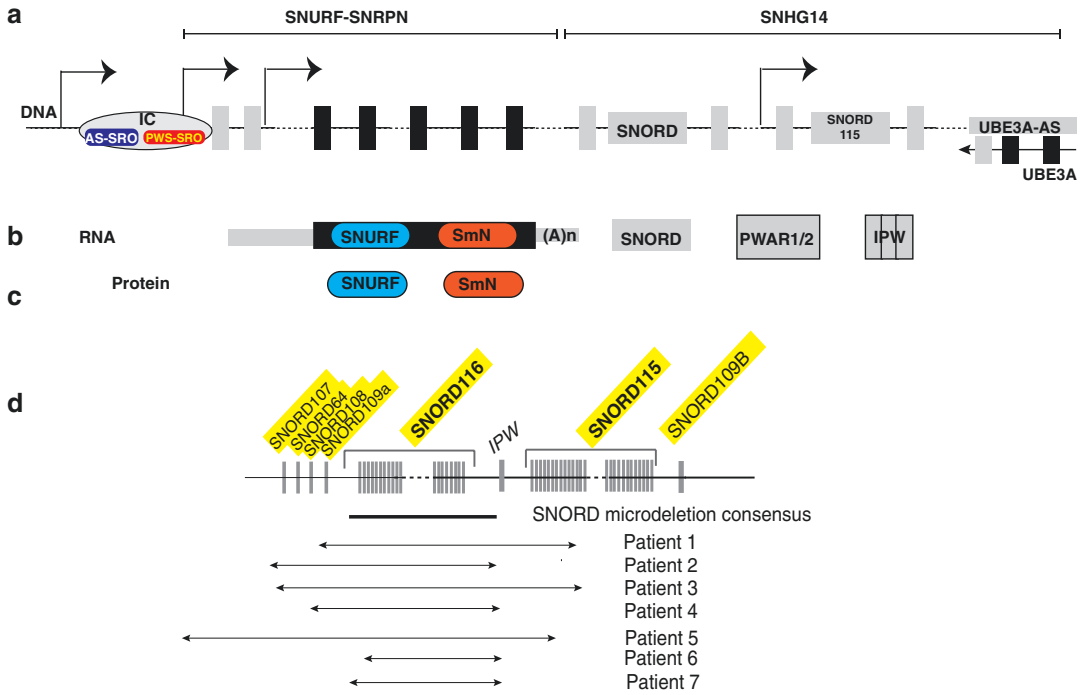

Fig. 2.5 The SNURF-SNRPN transcriptional unit. (**a**) Overview. The SNURF-SNRPN transcription unit comprises at least 600,000 nucleotides. It starts with at least three promoters (arrows) initiating at three start sites, one of which overlaps with the imprinting center. A further upstream promoter has been described in PWRN1 (not shown). The imprinting center (IC) is bipartite, defined by the Angelman smallest region of overlap (AS-SRO) and the PWS smallest region of overlap (PWS-SRO) that are responsible for the expression from the maternal and paternal allele, respectively. Protein coding exons are shown in black and noncoding exons in gray. (**b**) The SNURF-SNRPN gene creates a bicistronic mRNA that encodes the SNURF and SmN proteins. This mRNA is polyadenylated, leading to the termination of part of the transcript. 'Read-through', i.e. continuation of the transcript downstream of the polyadenylation site creates a large (>440,000 bp) 3'UTR, referred to as SNHG14 (small nuclear RNA host gene 14). SNHG14 hosts C/D box snoRNAs (SNORDs) that are located between two noncoding exons. In addition, noncoding transcripts are generated through splicing (IPW) or as intronless RNAs (PWAR1, 2). The SNHG14 transcript extends as an antisense transcript into the UBE3A gene that is expressed from the maternal allele. There is evidence for a neuron-specific promoter upstream of the SNORD115 cluster. (**c**) SNURF and SmN proteins are encoded by SNURF-SNRPN. (**d**) Overview of the SNORDs in SNHG14. Each SNORD expression unit consists of two noncoding exons flanking a SNORD located in the intron and is depicted as a single gray line. IPW is a spliced RNA consisting of three exons. Detailed genomic coordinates are given in [125, 126]

in brain and testis, exons from the upstream PWRN1 genes are joined to SNURF-SNRPN upstream exons, indicating that PWRN1 could be part of the SNURF-SNRPN transcription unit [47]. In general, the repressed maternal allele is heavily methylated, but there are region-specific differences. For example, one of the exons in the 5'UTR (exon U1B) is located in a CpG island that is extensively methylated on the repressed maternal allele and unmethylated on the expressed paternal allele. However, the reverse methylation pattern is seen in intron 5, that is, methylated in the paternal allele, but unmethylated in the maternal allele [58].

The coding SNURF-SNRPN mRNA contains two open-reading frames, SNURF and SNRPN, that both encode nuclear proteins [59] (Fig. 2.5c). Although SNURF is evolutionary highly conserved, its function is unclear. Its ORF contains a nuclear localization signal, as well as cAMP-dependent kinase, casein kinase, and protein kinase C sites [59].

The SNRPN open-reading frame encodes the SmN protein (Sm protein N, N for neuron), which

belongs to the LSm (like Sm) protein class. Sm proteins (from Smith after an autoimmune antiserum) form a heptameric ring around small nuclear RNAs [60]. There are seven ubiquitously expressed Sm proteins (SmB, D1, D2, D3, E, F, G). SmB can be replaced with an alternatively spliced variant, SmB' [61] or SmN. Together with the major snRNAs (U1, U2, U4, U5), Sm proteins form small nuclear ribonucleoproteins (snRNPs) that generate the spliceosome.

Of note, the SmN protein is different from the SMN protein (capital M), which is generated by the survival of motoneuron 1 (SMN1) gene [62]. SMN functions in loading the Sm proteins, including SmN onto snRNAs [63], but is not linked to the Prader-Willi gene region.

SmN is predominantly expressed in the brain and to a lesser extent in the heart [64]. Reflecting its ability to compete with SmB/B', the relative amount of SmB/B' is lowest in the heart and the brain. Whereas most Sm proteins are small, 16 kD or less, SmB and SmN are larger. Due to a long C-terminal extension, SmN is 28 kD. Overexpression studies showed that SmN expression leads to a reduction of SmB/B' protein, but not their respective mRNA levels, indicating a post-transcriptional regulatory mechanism. SmN is absent in brains from PWS subjects, which is compensated by an increase of SmB/B' [65].

SmN is incorporated predominantly into U2 snRNP and at higher cellular concentration also seen in U1 snRNPs [66]. Overexpression of SmN has little effect on overall gene expression, but it slightly influences alternative splicing of a few mRNAs, such as BIN1 and EXOC7 pre-mRNAs [67]. Mice lacking SmN show no changes in alternative splicing [68]. Thus, despite extensive molecular characterization, the physiological function of SmN and the effect of SmN substituting the SmB/B' proteins are not fully understood.

SNHG14: 3' UTR of the SNURF-SNRNP Transcript

The SNURF-SNRNP open-reading frames are followed by a large (>440,000 bp) 3' untranslated region (3' UTR), termed SNHG14 for small nucleolar RNA host gene 14. SNHG14 contains numerous nonprotein-coding RNAs, most prominently C/D box snoRNAs. The 3'UTR extends as an antisense RNA into the downstream ubiquitin protein ligase E3A gene (UBE3A) that is expressed from the maternal allele in the brain [69] (Fig. 2.5a).

The SNHG14 region is nearly devoid of H3K27Ac histone marks that indicate transcriptional start sites. However, CAGE tag analysis (5' tag analysis of gene expression) indicates start sites between SNORD116 and SNORD115 clusters [70] (Fig. 2.5a). It is thus possible that the SNHG14 transcripts originate from the various 5' as well as internal promoters. The SNHG14 transcript is extensively alternatively spliced and harbors multiple termination points. In addition to SNORDs, several noncoding RNAs are found in the SNHG14 primary transcript, including IPW (imprinted in PWS), PWAR1, and PWAR5 (Prader-Willi/Angelman region RNA) (Fig. 2.5b). Microdeletions of the SNORD116 cluster generate a phenotype that shares features with PWS, which emphasizes the role of SNORDs in PWS (Fig. 2.5d).

Role of C/D Box snoRNAs in PWS

General Features of C/D Box snoRNAs (SNORD)

Currently, at least 295 C/D box snoRNAs (SNORDs) have been identified [71]. However, most of our knowledge of SNORD function derives from studies performed on highly expressed SNORDs that act on ribosomal RNA (rRNA) biosynthesis. The biogenesis and function of SNORDs acting in rRNA synthesis are summarized below for a better understanding of the SNORDs in the PWS region that are far less understood [72].

snoRNAs are highly expressed RNAs, which is why they have been studied since 1979 [73] and are among the best characterized human RNAs. There are two main classes of snoRNAs – C/D box snoRNAs (SNORDs) that guide ribose

2'-O-methylation and H/ACA box snoRNAs (SNORA) that guide pseudouridinylation. A typical mammalian cell contains an estimated 200,000 copies of SNORD3 (U3) and 20,000 copies of SNORD13/14 [74, 75], which compares to an estimated 200,000 mRNA molecules in a cell [76]. SNORDs have characteristic structural elements: the C (RUGAUGA, R = purine) and D (CUGA) boxes, which are usually present in duplicates (C' and D' boxes) and up to two antisense boxes hybridizing to the RNA target [77]. SNORDs are flanked by two termini that form a stem in the final SNORD ribonucleoprotein complex (SNORNP) (Fig. 2.6a, c).

Biogenesis of Human SNORDs

With the exception of four SNORDs (U3, U8, U13, and U118), human SNORDs are located in introns [78, 79]. Generally, introns are released as lariats after the splicing reaction (Fig. 2.6b). The lariats are opened up by the debranching enzyme and are subsequently degraded through exonucleases where XRN1/2 acts on the 5' end and the RNA exosome at the 3' end [80, 81]. The close connection between pre-mRNA splicing and SNORD biogenesis is reflected by a distance requirement for SNORDs that are located around 33–40 nt upstream of the branch point, which was shown with biochemical studies using a few SNORDs [82, 83]. SNORDs associate with proteins in a snoRNP precursor, which prevents snoRNA degradation. In addition, the stem-termini forms a short dsRNA stem that protects from exonucleases. Four proteins, *NHP2L1* (*15.5k*, *SNU13*), *NOP56*, *NOP58*, as well as *fibrillarin* [84–86] that catalyzes 2'-O-methylation of target rRNAs, are then deposited on the snoRNP. The addition of proteins to the snoRNA is aided by the R2TP complex [named after the yeast proteins ATPases Rvb1 and Rvb2 (named after *E. coli* DNA repair enzyme ruvB), Pih1 (protein interacting with Hsp90), and Tah1 (TPR-containing protein associated with Hsp90) [87]. R2TP components are conserved from yeast to humans. Two of its members, PIH1D1 and RPAP3, shuttle between cytosol and nucleus [88]. The shuttling and the SNORD assembly are regulated in yeast by the nutritional status via phosphorylation emanating from the mTOR pathway [88].

Well-Understood "Classical" and Novel Functions of SNORDs

The best understood function of SNORDs is their involvement in rRNA biogenesis, where they participate in 2'-O-methylation, folding, and cleavage of pre-rRNA. rRNAs are made from a large precursor that contains tandem arrays of 18S, 5.8S, and 28S rRNA. rRNA undergoes extensive modification, including 2'-O-methylation, pseudouridinylation, and base modifications. SNORDs catalyze the 2'-O-methylation of at least 106 ribose sites in humans [89]. SNORDs bind to the nascent rRNA using interactions between their antisense elements and pre-rRNA, which positions the methylase fibrillarin to perform the 2'-O-methylation (Fig. 2.6c). It is possible that this process also influences the folding of the pre-rRNA. About 80 proteins are attached to the pre-rRNA during this step [90, 91].

In addition to 2'-O-methylation, several SNORDs including the most abundant U3 direct cleavage of the pre-rRNA [92]. Although U3 binds the methylase fibrillarin, it performs only cleavage of pre-rRNA.

About half of the known SNORDs, including all the SNORDs hosted by SNHG14, do not have predicted rRNA targets and are considered "orphan" [79, 93], suggesting novel functions other than noncoding RNA methylation or cleavage.

Outside PWS, there is a growing list of diseases associated with a loss of SNORD expression that does not lead to detectable changes in rRNA processing. Examples include several forms of cancer [94–103], cancer progression [104], cardiovascular disease [105], lipotoxic stress [106], osteoarthritis [107], cerebral microangiopathy leukoencephalopathy [108], diabetic glucose deregulation [109], and viral host interactions [110].

Biochemical analyses showed that about 1/3 of highly expressed SNORDs form protein

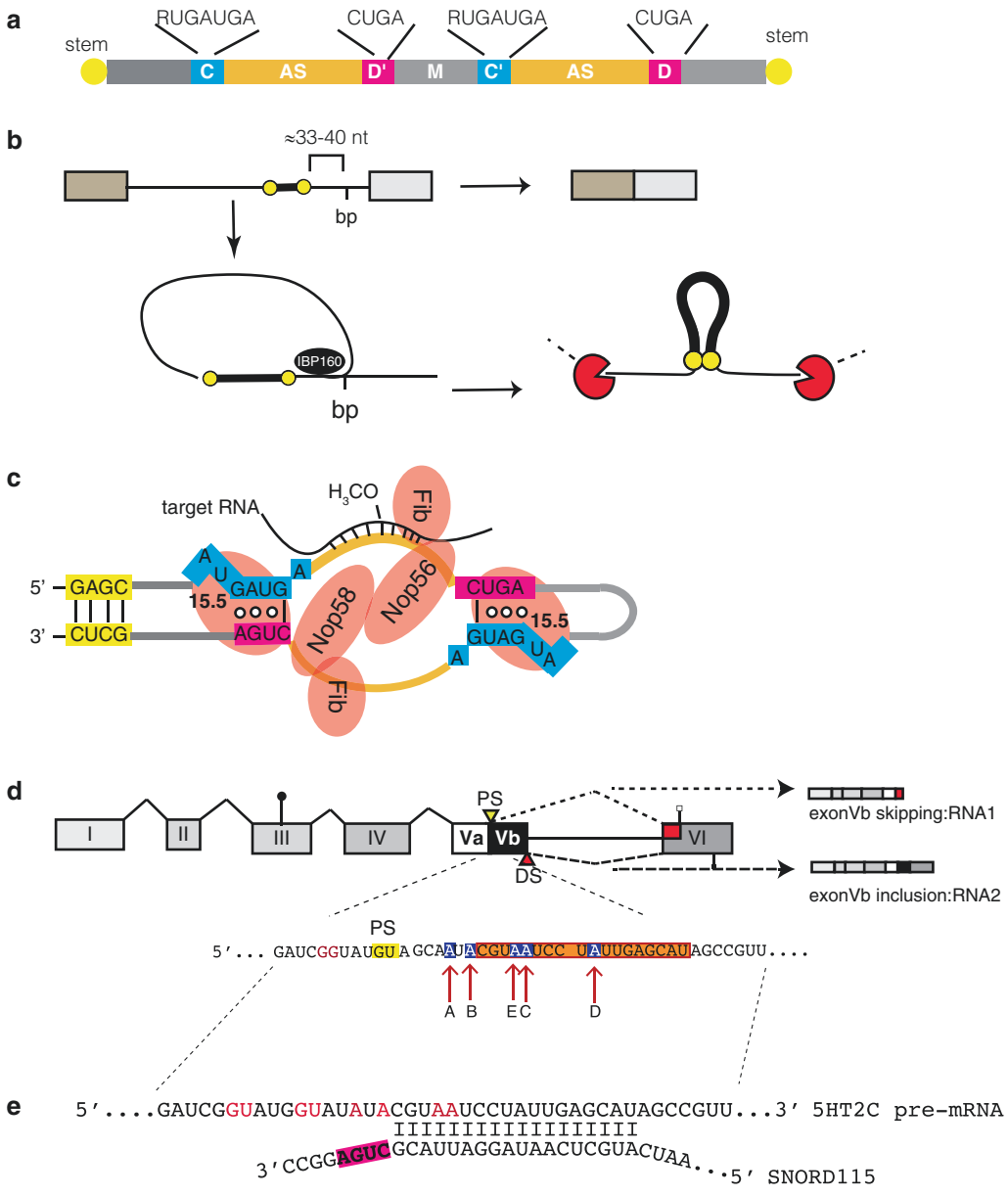

Fig. 2.6 Structure and biogenesis of SNORDs and base complementarity between SNORD115 and 5HT2C. (**a**) A typical SNORD is characterized by C and D boxes that are present in duplicates (C' and D'), flanked by two terminal sequences that form a short stem. AS: antisense boxes, that is, SNORD sequences that bind to target RNAs. (**b**) SNORDs (thick black line with yellow dots) reside in introns (line) flanked by two exons (boxes). The splicing reaction generates a lariat that contains the SNORD. Often, there is a distance requirement between the SNORD and the branchpoint, which reflects the binding of a protein. After debranching of the intron, exonucleases (red circles) trim the SNORD up to the stem structure that protects the snoRNA. (**c**) Structure of the SNORD-protein complex. A stem of four basepairs is shown; this stem can vary in structure and size. Proteins (15.5, NOP58 and NOP56, and fibrillarin) that associate with the snoRNA are indicated as round ovals. The interaction with the target RNA is schematically shown; a specific residue five nucleotides downstream of the C box is modified by fibrillarin that adds a methyl group to the 2'-hydroxyl group on the ribose. (**d**) Schematic structure of the serotonin receptor 2C (5HT2C) pre-mRNA. The start codon in exon III is indicated. Exon Vb is alternatively spliced due to a proximal (PS) and distal (DS) splice site. Skipping of exon Vb results in RNA1 that encodes a protein residing in intracellular compartments. Vb inclusion generates a full-length receptor. A partial sequence of exon Vb is shown underneath, and the proximal splice site is highlighted in yellow. The 5HT2C pre-mRNA is edited at five sites (A–D), which changes an adenosine to inosine. (**e**) Base complementarity between SNORD115 and exon Vb

complexes with and without fibrillarin, suggesting functions outside of 2'-O-methylation. It was shown that SNORD27 regulates alternative splicing in addition to its well-documented role in rRNA methylation. Fibrillarin-free, nonmethylating SNORDs likely act similar to RNA oligonucleotides, that is, they can recognize targets using their entire sequence, not just the antisense boxes [111]. In addition, SNORDs participate in polyadenylation of RNAs [112, 113].

SNORDS of the PWS Region

All SNORDs in the PWS region are hosted by the SNHG14, that is, the 3' UTR of the SNURF-SNRPN gene (Fig. 2.5a, b). Each SNORD is localized in an intron flanked by two noncoding exons that have canonical 5' and 3' splice sites [114], (Figs. 2.5a and 2.6b). With the exception of SNORD115, no RNA targets have been identified for the SNORDs in the SNHG14 region.

Very little is known about SNORD107, SNORD108, SNORD64, and SNORD109A, B. These SNORDs are predominately expressed in the brain, but they can also be detected in other tissues tested using RT-PCR [70, 115]. SNORD109A and 109B have identical sequences, but these are hosted by two different introns.

SNORD116

SNORD116 is present in at least 28 tandemly arranged copies. The copies are dissimilar and fall in at least three clusters [115]. SNORD116 is strongly expressed in the brain, but it can be detected by Northern blot and RT-PCR in all tissues. The weakest expression is found in the muscle, liver, and placenta [70].

In contrast to all other SNORDs of the region, the C' box of all SNORD116 copies deviates from the consensus RUGAUGA and is RTGA**G**TGA. This deviation is evolutionary conserved [116]. Reflecting SNORD116's dependency on splicing (Fig. 2.6b), its formation in the cellular model system is dependent on optimal splice sites [117] and presence of neuron-specific splicing factors in mice [118]. The exons surrounding the SNORD116 copies are joined in a large RNA that forms an "RNA cloud" that resides near sites of transcription and increases during sleep in the mouse brain [119].

Overexpression of a single SNORD116 copy in cells showed about 200 changes in mRNA expression. Changes in gene expression were often increased when SNORD115 was co-expressed, indicating a possible interaction between these SNORDs. However, no binding sites could be identified in putative target genes [117]. A comparison between neurons made from PWS subject and control-derived iPS cells identified a different expression of nescient helix loop helix 2 (NHLH2) and the prohormone convertase PC1, as reflected in a SNORD116 knockout mouse model [120]. However, no direct RNA:SNORD116 interaction could be identified.

Microdeletions of the SNORD116 region have been identified in seven individuals that exhibit a Prader-Willi-like phenotype [121–126] that is less severe than the phenotype caused by loss of expression from the full Prader-Willi region between BP1 and BP3. Comparing all microdeletions identifies a region containing SNORD116 and IPW, suggesting that the loss of these SNORDs plays a central role in PWS disease etiology [121–127] (Fig. 2.5b). Mice lacking SNORD116 recapitulate some of this phenotype as they show postnatal growth retardation and an increased food intake, which is compensated by higher energy expenditure [128] and can be reversed by reintroducing SNORD116 [129, 130]. In addition, SNORD116 mice show a deregulation of dysregulation of diurnally expressed Mtor and circadian genes Clock, Cry1, and Per2 [119], and in diurnal DNA methylation in mouse cortex [131].

SNORD115

SNORD115 is present in 48 tandemly arranged almost identical copies. SNORD115 is expressed almost exclusively in the brain, but smaller amounts can be detected in the kidney, liver, and

muscle [70]. It is the only SNORD of the SNHG14 transcript with a known target RNA, as it shows an 18 nt complementarity to a known RNA, the alternative exon Vb of the serotonin receptor 2C (5HT2C) (Fig. 2.6d). Skipping of these alternative exons leads to a truncated 5HT2C receptor. In addition, exon Vb undergoes RNA editing at five sites, where an adenosine is deaminated into an inosine.

The 5HT2C receptor regulates food uptake in the arcuate nucleus. 5HT2C activity induces POMC (pro-opiomelanocortin), which is processed into alpha MSH that reduces food intake by acting on neurons in the paraventricular nucleus. The full-length 5HT2C, containing exon Vb, is constitutively active, that is, it signals without ligand binding. RNA editing changes 5HT2C's amino acids, reducing the receptor's coupling to G-proteins, which strongly reduces the constitutive activity. Skipping of exon Vb results in a truncated 5HT2C receptor that resides in the endoplasmic reticulum and does not reach the plasma membrane. The truncated receptor can heterodimerize with the full-length receptor, leading to a sequestration of the 5HT2C inside the cell, and a reduction of 5HT2C signaling. RNA oligonucleotides mimicking the exon-skipping effect of SNORD115 strongly reduce food intake in mice [132].

Transfection studies using reporter genes in cells showed that SNORD115 promotes the inclusion of exon Vb [133] due to direct SNORD:mRNA interaction. SHAPE assays showed that the serotonin receptor 2C pre-mRNA in this region forms a stable double-stranded structure that sequesters the regulated splice site, causing exon skipping [134]. Thus, SNORD115 appears to regulate the ratio between full-length and truncated 5HT2C receptors by influencing their alternative splicing.

In similar cell-based assays, SNORD115 was also shown to influence 2'-O-methylation of short RNAs corresponding to serotonin receptor 2C pre-mRNA when these RNAs are sent to the nucleolus by using reporter constructs with an RNA polymerase I promoter [135]. Exon Vb is included in most brain regions, with the exception of the choroid plexus, which also lacks expression of SNORD115. Overexpression of SNORD115 in choroid plexus does not promote exon Vb inclusion but has a modest effect on A->I editing [136].

PWS knockout mice lacking expression of the SNURF-SNURPN and SNHG14 region show a reduction in exon Vb inclusion in the arcuate nucleus and pituitary, indicating that SNORD115 could change splicing in the nucleoplasma [137, 138]. However, a recent CRISPR/Cas9 SNORD115 knockdown mouse did not show significant changes in 5HT2C alternative splicing and modest changes in 5HT2C RNA editing, which questions the cell-based data and the changes in mice with longer deletions [139]. Thus, despite a clear binding site and effects using reporter genes in cell models, the physiological role of SNORD115 remains elusive.

IPW

IPW stands for imprinted in Prader-Willi. IPW is a noncoding RNA that is part of the SNHG14 region transcript and contains two introns. Removal of the IPWs region in an iPS cell model showed surprisingly an upregulation of the imprinted *DLK1-DIO3* gene region on chromosome 14. This indicates that IPW downregulates maternally expressed genes of the *DLK1-DIO3* region [140] through an unknown mechanism.

The imprinted *DLK1-DIO3* region is important for fetal development and its deregulation in adult tissues can lead to cancer [141]. Its loss due to uniparental disomy leads to Kagami-Ogata syndrome [142]. The paternal allele expresses DLK1 and RTL1 and the maternal allele expresses GTL2, RTL1as, and MEG8 [143]. Loss of IPW leads to an upregulation of GTL2(MEG3), RTL1as, and MEG8 in cell models, but the molecular mechanism remains unclear.

GTL2/MEG3 is a noncoding RNA (maternally expressed only) that functions as a tumor suppressor, MEG8 is also a noncoding RNA that hosts two clusters of brain-specific C/D box snoRNAs (SNORD113 cluster and SNORD114 cluster), as well as numerous miRNAs, which is similar to the SNORD cluster in PWS [16].

Genes in Paternally Imprinted Region, Expressed in PWS, Not Expressed in Angelman Syndrome

Two genes UBE3A and ATP10A in the Prader-Willi region are imprinted on the paternal allele and thus only expressed from the maternal allele. Their loss of expression contributes to Angelman syndrome.

UBE3A

UBE3A is an E3A ubiquitin-protein ligase (UBE3A). Analysis in mouse shows that this gene is expressed only from the mother's allele in neurons, but it is likely expressed from both alleles in glia, that is, oligodendrocytes and astrocytes [11, 12] and thus the loss of the paternal allele expression in PWS could have an effect in these cells. UBE3A is in antisense orientation to SNHG14, which downregulates its expression [69, 144–146].

Functionally, UBE3A encodes the E3 ligase E6-associated protein (E6AP) that attaches ubiquitin to target proteins, resulting in their degradation. Targets have been shown to be p53, Arc, Ephexin5, and SK2 [147].

ATP10A

ATP10A is an ATPase phospholipid transporting 10A protein, a P4-type ATPase, acting as a lipid flippase. It is a membrane protein that transports phosphatidylcholine across membranes, ensuring a different composition of lipid bilayers. Its overexpression in cells influences cell shape and size, cell adhesion, and spreading [148].

Nonimprinted Genes Between BP1 and BP2

These genes are biallelically expressed, but they are deleted in type I deletion patients, making it possible that their expression levels are reduced (Fig. 2.1). Microdeletions between BP1 and BP2 cause Burnside-Butler syndrome characterized by developmental delays, language impairment followed by motor delay, attention-deficit disorder/attention-deficit hyperactivity disorder, and autism spectrum disorder [3, 149, 150].

NIPA1

NIAP1 is an abbreviation for nonimprinted in Prader-Willi/Angelman syndrome region protein 1. The protein encodes a magnesium transporter that associates with early endosomes and the cell surface. This localization is magnesium dependent: a high magnesium concentration promotes localization in endosomes. Mutations in NIPA1 cause autosomal-dominant hereditary spastic paraplegia (HSP), a neurodegenerative disorder characterized by progressive lower limb spasticity and weakness [151].

NIPA2

NIPA2 is an abbreviation for nonimprinted in Prader-Willi/Angelman syndrome region protein 2. Similar to NIPA1, this protein is also a magnesium transporter that maintains magnesium influx [152]. NIPA2 is downregulated in mouse models of diabetes and promotes osteoblast function, likely by influencing mitophagy, that is, the selective degradation of mitochondria due to autophagy [153].

CYFIP1

CYFIP1 stands for cytoplasmic FMR1 interacting protein 1 (FMR1: fragile X mental retardation protein). A subgroup of fragile X syndrome patients shows a Prader-Willi-like phenotype with obesity and hyperphagia. In 13 cases of fragile X-syndrome with Prader-Willi phenotype investigated, CYPFIP1 mRNA was reduced [154].

Reflecting its association with CYFIP1 inhibits local protein biosynthesis. In addition, CYFIP1 is a component of the WAVE regulatory complex

that regulates actin polymerization. In the WAVE complex, CYFIP1 is often called SAR1.

CYFIP1 also interacts with the small GTPase Rac1 and localizes in synaptosomes [155]. Induced by BDNF (brain-derived neurotrophic factor) Rac1 causes a conformational change of CYFIP1 that releases CYFIP1 from translational initiation factors and promotes its association with the WAVE complex and actin polymerization. Through this mechanism, CYFIP1 contributes to the formation of dendritic spines [156].

TUBGCP5

TUBGCP5 is tubulin gamma complex-associated protein 5. The gamma tubulin ring complex is a large protein complex that nucleates microtubules to the centrosome [157]. Centrosomes are the main microtubule-organizing center in the cell [158]. TUBGCP5, also named KIAA1899, is expressed in all tissues, including the brain [159].

Nonimprinted Genes Between ATP10A and BP3

GABRB3, GABRA5, GABRG3

The region contains three genes encoding subunits of the GABA A receptor, namely, GABRB3 (beta3 subunit), GABRA5 (alpha 5 subunit), and GABRG3 (gamma 3 subunit). The GABRG3 locus also expresses a spliced, noncoding antisense transcript GABRG3-A3. The GABA A receptors are the major inhibitory receptors in the brain, responding to GABA (gamma amino butyric acid). Each receptor is formed by five subunits that form a chloride channel. Currently, 19 subunits are known. GABA A receptors are a common drug target, most notably for benzodiazepines [160].

OCA2

OCA2 is an abbreviation for oculocutaneous albinism, type 2. Mutations in this gene lead to oculocutaneous albinism, which affects the eyes (oculo-) and skin (-cutaneous). The gene is the homolog of the mouse pink-eyed dilution (p) locus and encodes a transmembrane protein with 12 membrane-spanning domains [161]. Melanosomes lacking OCA2 have a higher pH than wild-type melanocytes, suggesting that OCA2 regulates the pH of melanosomes. It is not fully understood how this change in pH leads to a loss of melanin, which could occur either by inhibiting melanin synthesis or the uptake of tyrosine, the substrate for melanin synthesis [162]. The hypopigmentation seen in PWS is likely linked to the hemizygosity of OCA2, as one copy is lost due to the deletion [163]. Since the pink-eyed dilution (p) locus in mouse shows recessive inheritance, it is possible that other modifying genes act on OCA2 [162].

HERC2

HERC2 stands for HECT and RLD domain-containing E3 ubiquitin protein ligase 2. It contains a C-terminal HECT domain and homologous to E6-AP C terminus that catalyzes the transfer of ubiquitin from E2 ligases. HERC2 also contains an RLD domain, which stands for regulators of chromatin condensation 1 (RCC)-like domain. The RLD domain has a twofold function: it acts as a guanine nucleotide-exchange factor (GEF) for the small GTPase Ran and also interacts with histones H2A and H2AB that are bound to chromatin [164]. In addition, the protein contains a cytochrome b5-like region, a mind-bomb/HERC2 (M-H) domain, a CPH domain, a ZZ-type zinc finger, and a DOC domain. Reflecting the multiple domains, the protein interacts with more than 300 other proteins and likely serves as a scaffold to integrate protein complexes involved in protein transport, metabolism, and translation [165]. HERC2 binds to UBE3A via its HERC2-binding domain (Fig. 2.2e) [166]. The best understood functions are in DNA repair and replication. HERC2 is expressed in most tissues and throughout the cell, but it associates with the centrosome. HERC2 deletion in mice leads to reduced growth, jerky

gait, male sterility, female semisterility, and maternal behavior defects known as *rjs* (runty, jerky, sterile) mice [167].

Nonimprinted Genes Between BP3 and BP5

Defects in genes between BP4 and BP5 are extremely rare but have been reported. APBA2 is a gene found in this region.

APBA2 is the amyloid beta A4 precursor protein-binding family A member 2. The protein acts as a scaffold regulating the generation of β-amyloid [168, 169].

CHRNA7

CHRNA7 is the neuronal acetylcholine receptor subunit alpha-7. The gene is ubiquitously expressed, included in most brain regions. Acetylcholine receptors are composed of 5 subunits and 11 subunits are expressed in the brain. Changes in CHRNA7 expression are associated with schizophrenia, bipolar disorder, ADHD, and epilepsy [170].

Contribution of Genes to PWS

A tremendous amount of work has been done regarding genes expressed in the Prader-Willi region. Not a single gene stands out as the sole contributor to PWS. Five genes that work in the ubiquitination of proteins could affect hundreds of proteins. Similarly, the noncoding RNAs probably have multiple targets. It is thus likely that the loss of expression of numerous genes acts together to create the syndrome, which needs to be taken into account for any therapeutic intervention.

Databases

The piRNA database can be visualized at http://regulatoryrna.org/database/piRNA/genome.php.

Genes and their annotation can be visualized at http://genome.ucsc.edu.

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3 Laboratory Testing for Prader-Willi Syndrome

Nicole L. Hoppman, Elena Repnikova, and Ross A. Rowsey

Introduction

In 1981, Ledbetter et al. described a cytogenetically visible deletion of proximal 15q in four patients with Prader-Willi syndrome (PWS) [1]. Using several chromosome staining methods to evaluate chromosome 15 short arm variants, Butler and Palmer soon after showed that the PWS deletion preferentially involves the paternally inherited chromosome 15 (6134086). It was not until a few years later, however, that the mechanism behind this parent-of-origin effect became clear, when Nicholls et al. performed restriction fragment length polymorphism (RFLP) analysis in two patients with PWS who did not exhibit a 15q deletion. This was the first description of uniparental disomy (UPD) in PWS, and the authors concluded that genetic imprinting in this region must play a causal role in both PWS and Angelman syndrome (AS) [2]. It is now well known that paternal 15q11.2q13 deletion accounts for approximately 65%–75% of individuals with PWS, while maternal UPD accounts for about 20% to 25% of PWS. Only 1–2% of PWS individuals have a rarer type of mutation, including point mutations/microdeletions involving the imprinting center (IC), epimutation, or a chromosome rearrangement involving the 15q11.2q13 region [3–5].

As genetic analysis techniques have become more sophisticated over time, the genomic structure and gene content of the region of 15q commonly deleted in patients with both PWS and AS have been elucidated. This approximately 5–6 megabase genomic region is complex, containing both maternally and paternally imprinted genes as well as imprinting control centers (ICs) that regulate the expression of the imprinted genes. Nonimprinted genes are included within this region as well. Of importance, this region is flanked by segmental duplications that predispose the region to aberrant recombination events during meiosis, which explains both why most patients with PWS due to 15q deletion have nearly identical deletions, and how nearly identical deletions reoccur as de novo events at a somewhat frequent rate [6, 7] (Fig. 3.1). The majority of PWS patients have been demonstrated to have either a type 1 (breakpoint 1-breakpoint 3, genomic coordinates GRCh37/hg19 chr15: 22,876,632-28,557,186) or slightly smaller type 2 (breakpoint 2-breakpoint 3, genomic coordinates GRCh37/hg19 chr15: 23,758,390-28,557,186) deletion, which differ in size by an approximately 500 base

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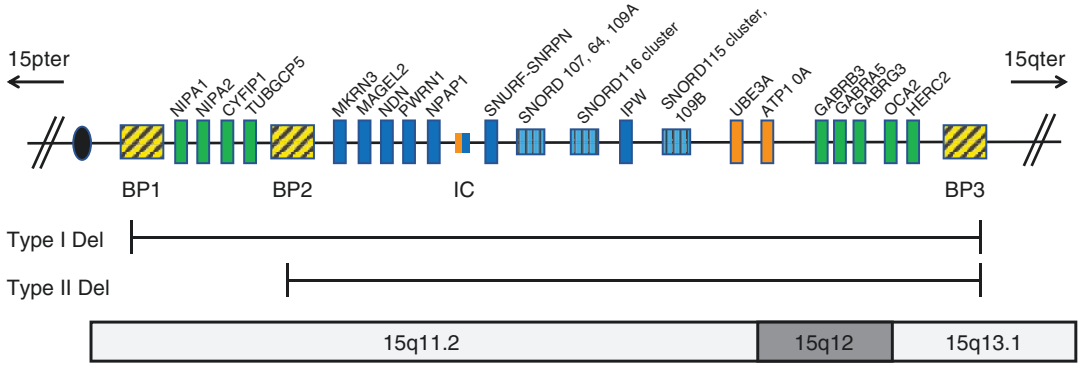

Fig. 3.1 Schematic of the Prader-Willi-Angelman syndrome region on chromosome 15. Nonimprinted genes are shown in green, maternally imprinted genes are shown in blue, and paternally imprinted genes are shown in orange. Regions of homology (segmental duplications) are represented by yellow hashed rectangles. The two common, segmental duplication-mediated deletions are depicted by horizontal lines. The black oval denotes the chromosome 15 centromere. Please note that the figure is not drawn to scale, and some genes are not shown for simplicity

pair pericentromeric region (breakpoint 1-breakpoint 2) that does not appear to contain imprinted genes [8] and is therefore not considered to be part of the Prader Willi-Angelman syndrome critical region, or PWASCR, which lies between breakpoints 2 and 3. The critical region contains nonimprinted genes, paternally imprinted genes, maternally imprinted genes (*MKRN3, MAGEL2, NECDIN, SNURF/SNRPN, NPAP1*, a cluster of C/D box small nucleolar RNA genes, *IPW*), and a handful of antisense transcripts. Over time, as patients with PWS with smaller, atypical deletions within this critical region have been described [9–16], the gene(s) responsible for the phenotypic features in PWS patients are closer to becoming revealed. The smallest region of overlap appears to have been pinpointed to an approximately 4.3 kilobase region that includes the CpG island, exon 1, and a fraction of intron 1 of *SNURF-SNRPN* [17]. It is generally believed that PWS is a contiguous gene syndrome and that the phenotypic features are likely caused by the loss of expression of multiple maternally imprinted genes within this region; however, specific genotype/phenotype correlations have yet to be definitively established.

As the mechanisms of pathogenesis underlying PWS have been resolved over time, clinical laboratory testing has also matured. Cytogenetic testing was first utilized, starting with karyotype and later fluorescence in situ hybridization (FISH) using a probe specific to the PWAS critical region. However, these assays can only reliably detect deletions, giving them a sensitivity of only approximately 70%. In the early 1990s, after the discoveries of both restriction enzyme digest sites at imprinted loci within the critical region as well as the development of a hybridization probe (PW71B) [18, 19], many laboratories adopted Southern blot as a first-tier "molecular" assay for clinical laboratory diagnosis of PWS, and this gradually replaced cytogenetic technologies as the "gold standard" for PWS testing due to its ability to detect both deletions and abnormal methylation patterns, the latter of which can be caused by either UPD or (rarely) IC mutations. Currently, most clinical laboratories have replaced Southern blot methodologies with alternative molecular methodologies such as methylation-sensitive multiplex ligation-dependent probe amplification (MS-MLPA) or methylation-specific polymerase chain reaction (MS-PCR), which are faster, less laborious, and higher throughput yet retain the ability to detect both deletions and uniparental disomy [20]. Some newer technologies such as MS-MLPA can even distinguish between deletion and copy-neutral events such as UPD.

Table 3.1 Recurrence risks associated with mutations that cause Prader-Willi syndrome

Mutation type	% of PWS patients	Recurrence risk
Deletion[a]	65–75%	<1%
Maternal UPD 15[b]	20–25%	<1%
IC mutation	<1%	Up to 50%
Balanced chromosome rearrangement	<1%	<1% to 100%[c]
Unbalanced chromosome rearrangement	<1%	Up to 50%
Epimutation (no obvious IC mutation)	<1%	<1%

[a]Assumes deletion in the proband is one of the recurrent segmental duplication-flanked (type 1 or type 2) deletions. Atypical deletions may have higher recurrence risk
[b]Rare parental translocations such as Robertsonian translocations result in increased recurrence risk
[c]All balanced, non-Robertsonian translocations involving the PWASCR described to date have been *de novo*. Robertsonian translocations have significantly increased risk with a theoretical 100% risk in the rare case of a 15;15 translocation

In general, there are three main reasons to perform molecular testing for PWS. The first is to establish or confirm a diagnosis, particularly in individuals who have nonclassic/atypical phenotypes or are too young to fulfill diagnostic criteria for PWS. Second, it is important to determine the mechanism of pathogenicity in order to determine recurrence risk and recommend the appropriate parental follow-up studies, as recurrence risk can vary from <1% to a theoretical value of 100% (Table 3.1). Finally, elucidation of the mutational cause of PWS in a proband enables accurate prenatal testing in those families with elevated recurrence risk.

Clinical Laboratory Testing for Prader-Willi Syndrome

Given the multiple different mechanisms that cause Prader-Willi syndrome, various techniques have been developed by clinical laboratories for the purposes of detecting these abnormalities. Currently, the most commonly utilized diagnostic tests for PWS include MS-MLPA, MS-PCR, microsatellite analysis, and single-nucleotide polymorphism (SNP)-based microarray. Each of these methods has

Table 3.2 List of laboratory methods utilized by clinical laboratories to establish a molecular diagnosis of PWS, depicting the advantages and disadvantages of each

Method	Advantages	Disadvantages
MS-MLPA	Rapid turnaround time, detects ~99% of PWS cases, including cases with deletions and abnormal methylation due to IC deletions or UPD	Not sensitive for mosaic cases; does not determine mechanism for detected abnormal methylation pattern (IC mutation vs. UPD) or rule out structural abnormality of chromosome 15
MS-PCR	Rapid turnaround time, detects ~99% of PWS cases	Does not establish etiology for abnormal methylation pattern; may give false-negative results due to SNPs at primer binding sites; requires bisulfite treatment
Microsatellite analysis	Detects ~25% of PWS cases (caused by UPD), differentiates between heterodisomy and isodisomy	Requires parental samples and only limited to cases caused by UPD. Requires follow-up testing to etiology of PWS if negative
Microarray analysis	Detects ~70% of PWS cases (those caused by large deletions); detects regions with loss of heterozygosity that may indicate UPD	Not diagnostic for UPD-related cases, does not detect all IC deletions or UPD-related cases; requires follow-up methylation analysis for UPD confirmation and determination of parent of origin and chromosome analysis for the mechanism
Chromosome and FISH analysis	Detects ~70% of PWS cases (those caused by large deletions). Detects structural abnormalities (e.g., Robertsonian translocation) involving chromosome 15	Not diagnostic for UPD-related cases, does not detect IC deletions or cryptic microdeletions; requires follow-up methylation analysis for UPD confirmation and determination of parent of origin

(continued)

Table 3.2 (continued)

Method	Advantages	Disadvantages
Southern blot	Detects ~99% of PWS cases	Uses radioactivity, requires a large amount of high-quality DNA, 2–3 weeks turnaround time; limited by enzyme restriction sites analyzed; false positives due to incomplete restriction digestion; may not be able to detect small IC deletions; does not determine etiology of PWS
Pyrosequencing	Detects ~99% of PWS cases; will detect epimutation at *SNRPN* locus	Does not determine etiology of PWS
Digital Droplet PCR	Detects ~3% of PWS cases caused by IC deletions and epimutation, cost-effective, low-input amount (25–50 ng) of DNA	Does not detect the majority of PWS cases
WES/WGS	Can detect 100% of PWS cases (theoretical)	Costly, long turnaround times

advantages and disadvantages (Table 3.2). Analysis of both methylation and copy number of the critical region in one assay is the most sensitive method that allows to diagnose over 99% of patients with PWS as well as distinguish PWS from AS in deletion and UPD cases [20, 21]. However, methylation analysis may not always define the PWS molecular mechanism. Therefore, for many patients, a combination of multiple methods may be needed to establish a diagnosis of PWS and definitively determine the etiology.

Commonly Utilized Molecular Diagnostic Tests

Methylation-Specific MLPA

Currently, methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) is the most commonly used diagnostic test. Many diagnostic laboratories use a commercially available MS-MLPA kit available from MRC Holland (http://www.mrc-holland.com). The SALSA MS-MLPA Probe mix ME028-C1 Prader-Willi/Angelman contains 47 MS-MLPA probes with amplification products between 129 and 481 nucleotides. All of the probes interrogate copy number, while six MS-MLPA probes contain an HhaI recognition site and provide information on the methylation status of the 15q11.2q13 chromosomal region.

The MS-MLPA assay is performed in two reactions. The first reaction utilizes multiple probe pairs that are designed to anneal to genomic DNA immediately adjacent to each other. These probe pairs are located within the PWS critical region as well as outside of the region on chromosome 15. Control probe pairs on other chromosomes are also included for quality control and normalization purposes. If the probe pairs anneal correctly, they will be ligated together and then PCR amplified via the presence of primer sequences incorporated onto the ends of the probes. The amount of amplicon is compared to that of normal controls in order to establish dosage. The second reaction is nearly identical to that of the first reaction with the exception that genomic DNA is first digested with HhaI, which will only digest unmethylated restriction sites while leaving methylated restriction sites intact. Only the intact sites will be amplified by PCR, allowing the determination of methylation status within the PWS critical region [22].

One of the major advantages of MS-MLPA is that this assay can simultaneously assay both methylation status and copy number within the 15q11.2q13 region. (Table 3.3). Since multiple probe pairs are utilized spanning the critical

Table 3.3 Representative MS-MLPA data obtained using the MRC Holland kit

Probe	Normal-undigested	Normal-digested	Patient 1-undigested	Patient 1-digested	Patient 2-undigested	Patient 2-digested
NIPA1[a]	1.01		1.02		1.03	
TUBGCP5[a]	1.02		1.00		1.00	
MKRN3	1.00		0.52		0.93	
MAGEL2 exon 1	1.00		0.57		0.92	
MAGEL2 exon 1+	**1.01**	**0.98**	**0.49**	**1.01**	**1.08**	**2.04**
NDN	0.99		0.48		1.02	
SNRPN U1B	1.00		0.53		0.90	
SNRPN U1B	1.00		0.51		1.00	
SNRPN intron u2	0.93		0.50		0.93	
SNRPN intron u2	0.93		0.53		0.93	
SNRPN u5	0.99		0.44		0.99	
SNRPN u5	1.09		0.48		1.09	
SNRPN exon 3+	**1.03**	**1.01**	**0.54**	**0.99**	**1.03**	**2.01**
SNRPN exon 3+	**1.00**	**1.04**	**0.47**	**1.01**	**1.00**	**1.99**
SNRPN exon 3+	**0.93**	**1.00**	**0.51**	**1.02**	**0.93**	**2.03**
SNRPN exon 3+	**0.92**	**0.99**	**0.50**	**1.01**	**0.92**	**1.97**
SNRPN exon 3	1.08		0.49		1.08	
SNRPN exon 7	1.02		0.48		1.02	
SNORD116-1	0.90		0.55		0.90	
SNORD116-11	0.95		0.51		0.95	
SNORD116-23	1.04		0.52		1.04	
UBE3A exon 9	1.05		0.47		1.05	
UBE3A exon 4	0.98		0.55		0.98	
UBE3A exon 3	1.01		0.50		1.02	
UBE3A exon 2	1.00		0.50		1.09	
UBE3A exon 1	0.90		0.49		1.03	
UBE3A upstream	0.99		0.48		1.00	
ATP10A exon 15	1.04		0.48		0.93	
ATP10A exon 1	1.01		0.54		0.92	
GABRB3 exon 9	0.91		0.48		1.08	
GABRB3 exon 7	0.99		0.55		1.02	
OCA2 exon 23	1.08		0.52		0.90	
OCA2 exon 3	1.03		0.51		1.03	
APBA2[a]	0.99		0.99		0.97	

Probes are listed in order of genomic location along chromosome 15, and
[a]indicates probes located outside BP2 and BP3. Probes that are maternally imprinted are indicated in bold and a + next to the probe name. Patient 1 represents a patient with PWS due to 15q deletion, as indicated by the decrease in the ratio of probes in the undigested reaction to approximately 0.5 while the imprinted probes maintain a ratio of approximately 1. Patient 2 is a patient with PWS due to maternal UPD15, as indicated by normal ratio of the undigested reaction but a ratio of 2 for the imprinted probes in the digested reaction, suggesting two maternally methylated copies

region, MS-MLPA can also identify small IC deletions and microdeletions within the *SNORD116* cluster, which are rare causes of PWS [23]. UPD will also be detected by MS-MPLA; however, UPD cannot be definitively distinguished from an IC mutation by this assay. Therefore, follow-up microsatellite analysis is recommended to confirm UPD when abnormal methylation is detected in the absence of a deletion.

Because MS-MLPA investigates methylation status and copy number at several loci within the critical region, the risk of a false-positive or false-negative result is reduced. One common cause of probe "drop out" is the presence of SNPs at probe binding sites. Assays that utilize only one probe, such as Southern blot, suffer from this issue. MS-MLPA, on the other hand, evaluates 40+ probes; therefore, if one probe site "fails" due to the presence of a polymorphism at the probe binding site, or other technical reasons, there are many remaining probes to evaluate. Care should be taken, however, when single probe deletions are observed by MS-MLPA. In this situation, laboratories can consider either only reporting deletions that include two or more consecutive probes, repeating the assay, or investigating (typically using Sanger sequencing) the patient's genomic sequence at the probe binding sites.

MS-MLPA has high sensitivity and should yield a positive result in approximately 99% of PWS patients. However, as mentioned above, in the case of normal copy number and abnormal methylation, it will provide no further information regarding the disease mechanism, necessitating follow-up studies, which is important for determining recurrence risk. Furthermore, other techniques, such as MS-PCR and methylation-specific quantitative PCR, may be more sensitive in patients with low-level mosaicism for the abnormality, although this situation is extraordinarily rare.

Methylation-Specific Polymerase Chain Reaction (MS-PCR)

MS-PCR relies on the up-front treatment of patient DNA with sodium bisulfite, which converts only unmethylated cytosine residues to uracil [24]. At imprinted loci, this treatment essentially makes parent-of-origin changes in the patient's genomic DNA. PCR primer pairs are designed that are specific for the maternal and paternal alleles, and the post-amplification products are visualized on a gel to evaluate the presence/absence of the maternal and paternal alleles. The presence of only one, rather than both, is interpreted as abnormal [25, 26] (Fig. 3.2). However, the underlying mechanism must be established by other follow-up methods as the assay will yield an abnormal result in cases of deletions, UPD, and IC defects but cannot distinguish between them. Further testing commonly includes SNP microarray, FISH, or chromosome analysis to detect a deletion or a chromosomal rearrangement, and microsatellite analysis for confirmation of UPD.

Microsatellite Analysis

To distinguish between UPD and IC mutations, analysis of multiple microsatellites within the PWS critical region as well as microsatellites outside of the critical region should be considered [27–29]. Microsatellites are short stretches of DNA sequence (typically 1–5 nucleotides) tandemly repeated. Many microsatellites are polymorphic, making them useful for identity testing. DNA from the proband as well as both biological parents is required for UPD analysis so that the alleles identified in the proband can be compared to those of the parents, which is necessary to distinguish between biparental inheritance and UPD. Results are interpreted as follows, taking into account multiple microsatellites spanning the chromosome:

- If only one maternal allele is present for microsatellites within the critical region as well as proximal and distal loci, with the absence of paternal alleles, isodisomy for chromosome 15 is implied.
- If both maternal alleles are present in the absence of paternal alleles, heterodisomy is implied.
- Maternal inheritance only within the critical region, with both maternal and paternal alleles

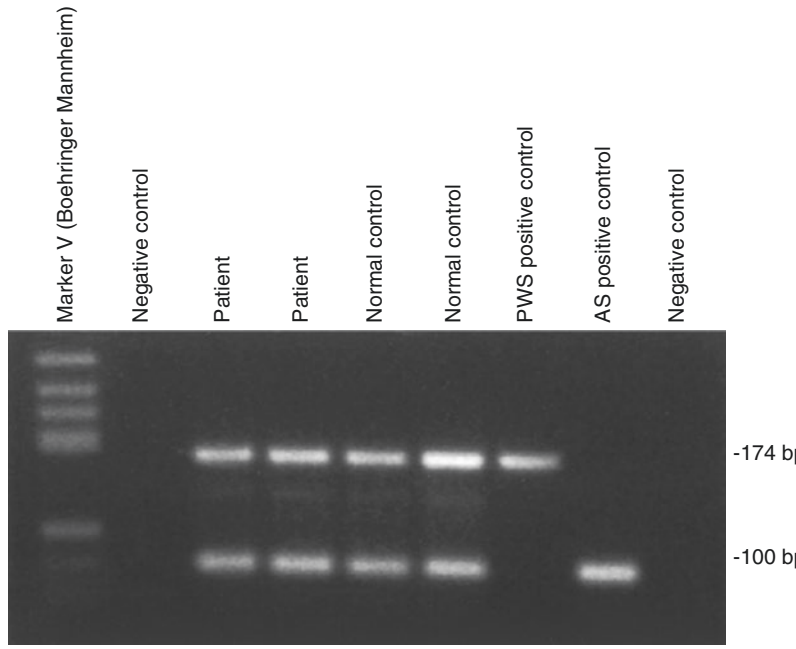

Fig. 3.2 Methylation-specific PCR analysis of the SNRPN promoter. Lane 1 (far left): size standard (marker V, Boehringer Mannheim). Lane 2: no DNA or negative control. Lanes 3–4: patients analyzed for Prader-Willi syndrome (PWS); both are normal as demonstrated by the presence of both the maternal (174 bp) and paternal (100 bp) bands present. Lanes 5–6: normal controls. Lane 7: PWS positive control showing lack of the paternal band. Lane 8: AS positive control showing lack of the maternal band. Lane 9 (far right): no DNA or negative control

present in the flanking regions, implies a deletion is present.

- Presence of both maternal and paternal alleles within the critical region and outside of the critical region could indicate IC deletion or point mutation if the diagnosis of PWS is accurate.

Several microsatellites within and adjacent to the critical region can be used for this analysis [27, 30]. For reagent and cost savings, microsatellites can be amplified by multiplex PCR using fluorescence-labeled primers and analyzed on an automated capillary electrophoresis instrument. Alternatively, PCR products can be radioactively labeled and analyzed by polyacrylamide gel electrophoresis; however, this method is labor-intensive, relatively low-throughput, and utilizes potentially toxic reagents. Therefore, very few clinical laboratories currently utilize this alternative method.

Microarray

Chromosomal microarray has a high sensitivity for detecting submicroscopic copy number variation in the form of deletions and duplications [31]. There are two main types of microarrays employed by diagnostic laboratories currently: comparative genomic hybridization (CGH) microarray and copy number+single nucleotide polymorphism (SNP) microarray. CGH microarray compares the DNA of a patient with that of a normal control. It detects copy number changes (in areas with adequate probe coverage) in sizes ranging from several kilobases to several megabases/whole chromosome. Therefore, the recurrent 15q11.2q13 deletions that cause PWS should easily be detected by CGH microarray, and depending on probe density, smaller and atypical deletions within the critical region can also be detected. However, platforms that do not evaluate SNP probes cannot detect UPD. The copy

number+SNP microarray technology allows detection of both copy number changes and copy-neutral absence of heterozygosity (Fig. 3.3a, b), the latter of which can be indicative of either UPD or identity by descent. Copy number+SNP microarray can detect approximately 66.7% of UPDs by identifying long (several Mb) contiguous stretches of homozygosity limited to chromosome 15. However, the finding of a long stretch of homozygosity involving chromosome 15 should not be considered diagnostic of UPD when analyzing a proband alone and may only indicate identity by descent [32–34]. Follow-up testing is necessary for UPD confirmation and determination of parent of origin; MS-MLPA and microsatellite analysis are both acceptable methods. Finally, it is important to note that, failure to detect homozygosity by SNP microarray analysis does not exclude the possibility of UPD. In general, chromosomal microarray is *not* considered a first-tier test when clinical suspicion for PWS is high.

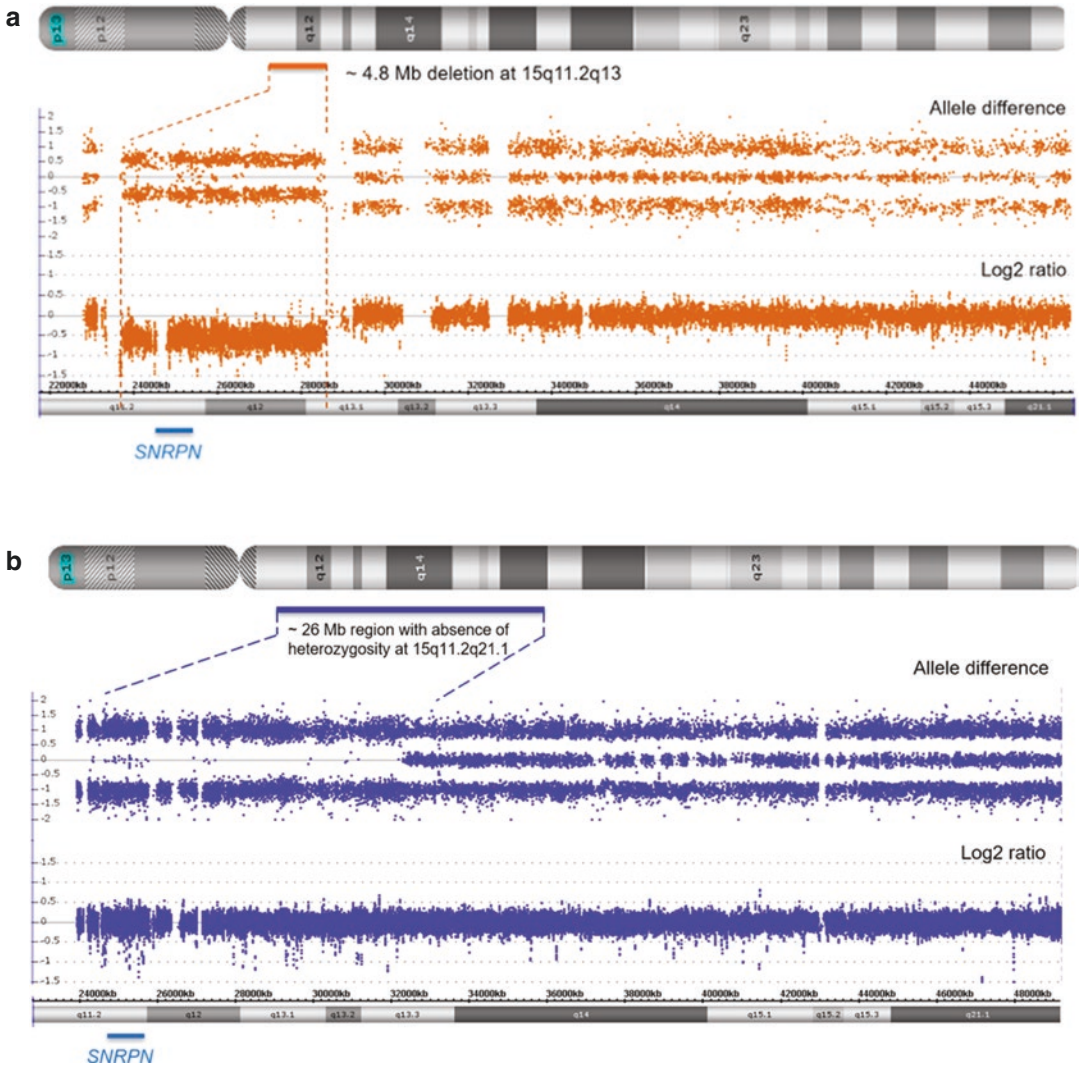

Fig. 3.3 (**a**) Thermo Fisher SNP array demonstrating a heterozygous, ~4.8 Mb deletion spanning the 15q11.2q13 region including the entire PWS critical region. (**b**) Thermo Fisher SNP array demonstrating ~26 Mb region with copy-neutral absence of heterozygosity encompassing 15q11.2q21.1. This result is suggestive of, but not diagnostic of, UPD15

Karyotype and FISH

Chromosome analysis, typically performed by G-banded karyotype, utilizes light microscopy to examine metaphase chromosomes that have been stained to produce a distinct banding pattern for each chromosome. This approach has a maximum resolution of 3–5 megabases (Mb) for structural anomalies and requires establishing a stimulated cell culture, usually using peripheral blood leucocytes, to obtain diving cells for analysis. FISH analysis uses fluorescent-labeled DNA probes to identify microdeletions and microduplications (Fig. 3.4) [35, 36].

Chromosome and FISH analysis will only yield a positive result in approximately 70% of individuals with PWS (those who have a 15q11.2q13 deletion or a rare structural chromosome rearrangement involving 15q11.2q13). In addition, neither technique can determine the parent of origin of a deletion when detected, necessitating follow-up studies when positive. Therefore, these techniques are very rarely used as a first-tier test for the diagnosis of PWS and are instead more commonly utilized to evaluate for the presence of a rare cause of PWS such as chromosomal translocation.

Alternative Techniques

A small number of laboratories use alternative methods of methylation analysis including Southern blot analysis, pyrosequencing, or digital droplet PCR [37]. Although these techniques have not currently widely utilized, they all have been successfully used within a diagnostic context. In recent years, next-generation sequencing has led to a significant increase of discovered genetic causes in both extremely rare and common disorders. The application of NGS in diagnostics of PWS provides a tremendous opportunity to identify all PWS-causing abnormalities; however, the wide application of this technology remains challenging for a variety of reasons, including but not limited to cost and insurance reimbursement.

Southern Blot

The first clinically available molecular test for Prader-Willi syndrome involved Southern blot analysis, a method still used in some molecular diagnostic laboratories (Fig. 3.5) [18, 19]. The Southern blot method begins with a restriction enzyme digest of genomic DNA, typically using two enzymes; one of which is methylation-sensitive. This results in the generation of maternal and paternal DNA fragments of different molecular weights. The digested products are separated by agarose gel electrophoresis and transferred to a nylon membrane, probed, and visualized. The method of visualization depends on how the probe is labeled; radioactive probes and chemiluminescence are two commonly utilized strategies.

Two of the major disadvantages of Southern blot analysis are the requirement for a large

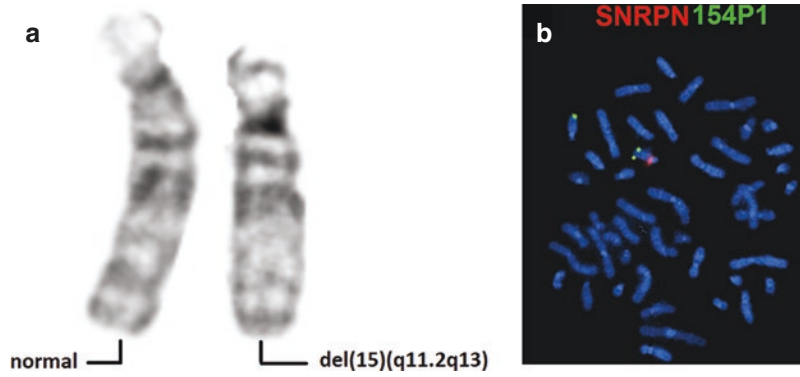

Fig. 3.4 (**a**) G-banded pair of chromosomes 15 with one normal homolog (left) and one homology with an interstitial deletion of the 15q11.2q13 region (right). (**b**) Metaphase cell hybridized with a *SNRPN* FISH probe (red) and a 154P1 control probe (green). Loss of one red signal indicates a deletion of the PWS critical region

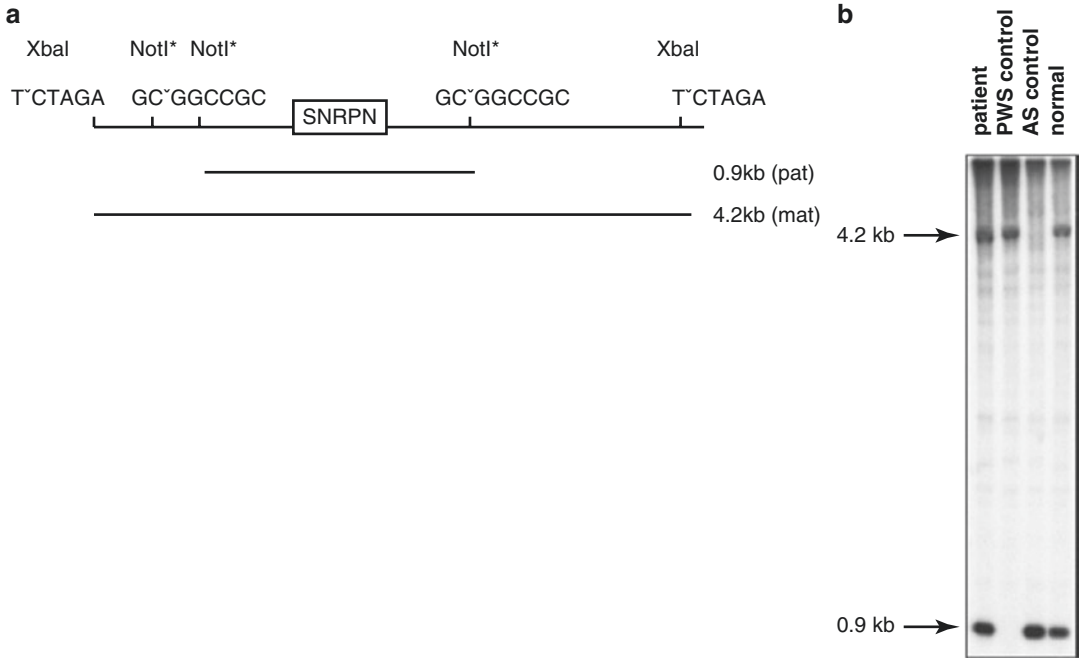

Fig. 3.5 (**a**) XbaI/NotI restriction map and RFLP sizes surrounding SNRPN probe68 (* indicates a methylation-sensitive restriction site for which the methylated allele will not be cut by the enzyme). (**b**) Autoradiogram of a Southern blot using the probe SNRPN with NotI and XbaI digested DNA. The patient analyzed is negative for Prader-Willi syndrome; both the 4.2 kb and the 0.9 kb DNA bands are present

amount of high quality (~ 5 mg), high molecular weight DNA, as well as that this assay only evaluated a single imprinted locus, which makes it more susceptible to false-positive and false-negative results when compared to methods such as MS-MLPA that interrogate multiple loci. In addition, many diagnostic laboratories are restricted in their use of radioactivity due to health and safety risks and are less likely to utilize radioactivity-based Southern blot analysis for PWS testing. Furthermore, Southern blot analysis does not distinguish between deletions, uniparental disomy, and IC defects. Therefore, reflex testing is required to define the mechanism of pathogenicity in order to accurately determine recurrence risk.

Pyrosequencing

Pyrosequencing, albeit less frequently utilized by diagnostic laboratories, is another methodology that can be used for quantitative methylation analysis of the *SNRPN* locus. This sequencing technology is based on the incorporation of a nucleotide into the template strand that leads to the release of pyrophosphate, which is quantified with a luciferase reaction. The signal produced is proportional to the amount of pyrophosphate released; therefore, methylation at CpG sites can be detected and quantified by analyzing the chemically induced C/T sequence differences with a specialized software [38] (Fig. 3.6). The methodology allows to quantify methylation status at CpG sites as well as detect epimutation at the *SNRPN* locus. Although pyrosequencing can only sequence a short stretch of nucleotides, it has several advantages over other assays. This methodology is similar to MS-PCR in terms of cost and time of analysis, yet it allows quantification of DNA methylation at multiple CpG sites as well as detecting epimutation at the *SNRPN* locus in a single assay. Pyrosequencing should also be capable of detecting rare cases of mosaicism [38].

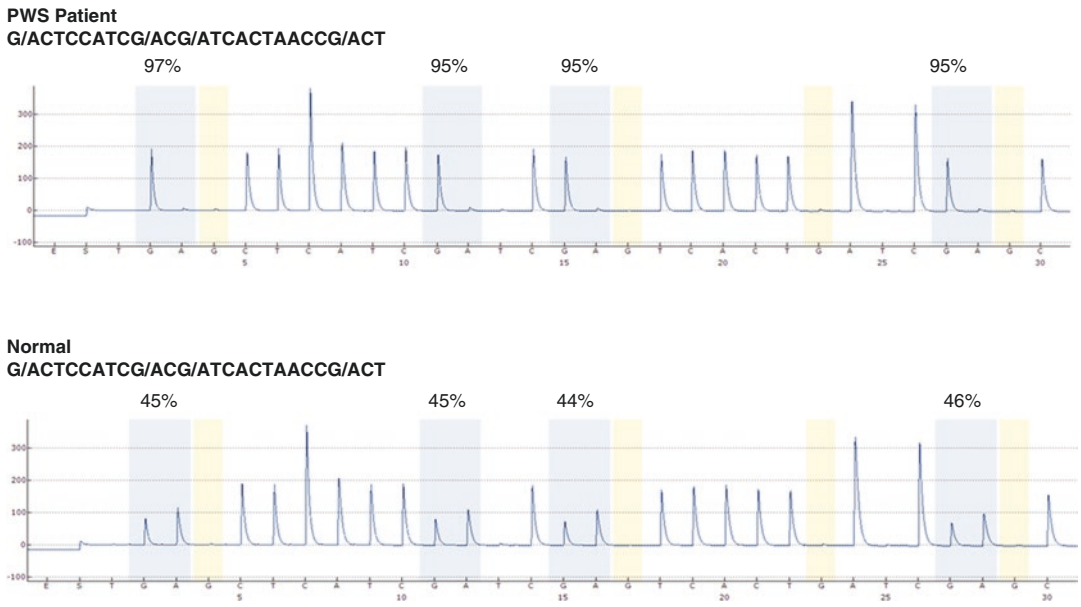

Fig. 3.6 Schematic diagram of a pyrosequencing assay showing the sequencing of a CpG island at the imprinting control region on chromosome 15. After bisulfite conversion, this region was sequenced on the PyroMark Q24 instrument (QIAGEN). Pyrograms are shown for a PWS patient and a healthy control. Blue shaded boxes represent possible methylation sites in which the nucleotide incorporated during pyrosequencing will depend on the methylation status of the C nucleotide in a CpG site (C = methylated and T = unmethylated after PCR; G/A, respectively, in the image due to the complementary strand being sequenced). Yellow shaded boxes represent a bisulfite treatment control of an unmethylated C nucleotide (PWS patient). The methylation status of the G allele is >94% at each methylation site in the patient sample indicating the presence of only the methylated (maternal) allele. This is consistent with a diagnosis of PWS (Normal). The methylation status of the G allele is ~45% at each methylation site along with the presence of an A allele in the blue shaded box. This is consistent with a normal methylation profile in which both the methylated (maternal) and unmethylated (paternal) alleles are present. (Courtesy of Raymond Caylor, PhD, Greenwood Genetic Center, Greenwood, SC, USA)

Digital Droplet PCR

Droplet digital PCR (ddPCR) is a method based on water-oil emulsion droplet technology. A sample is fractionated into thousands of droplets, and PCR amplification of the template molecules occurs in each individual droplet. ddPCR technology uses reagents and workflows similar to those used for most standard TaqMan probe-based assays. The clear advantage of this technology over other methods is that it can be used for copy number analysis of the sample with very little DNA (25–50 ng) from variably contaminated samples. Although it is not widely used for PWS testing by diagnostic laboratories, this assay is ideal for diagnostic use due to the low input requirement and its ability to generate results in a more cost-effective manner in comparison with other genetic testing options such as high-resolution microarrays, DNA methylation, and/or MS-MLPA, particularly to identify microdeletions within the IC region in those with PWS not caused by the larger typical deletions (type I or type II) or maternal UPD [37]. Hence, ddPCR may someday be adopted as a reflex assay for patients with PWS in whom a comprehensive assay such as MS-MLPA yields a negative result.

Whole-Exome/Whole-Genome Sequencing

Whole-exome and whole-genome sequencing (WES/WGS) are next-generation sequencing methods that continue to be used in increasing frequency as clinical diagnostic tools, particu-

larly in patients for whom targeted genetic testing has failed to identify pathogenic mutations. In recent years, WGS and WES have improved in their ability to detect a broader spectrum of variants, including small insertions and deletions, structural variants, and copy number variants (CNVs). WGS (with optimized bioinformatics tools) can theoretically detect all types of genetic abnormalities in a single experiment and can even be modified to assay methylation. WES and WGS are also attractive options in that they would allow for analysis of additional genes, such as those in which mutations cause syndromes that have significant phenotypic overlap with PWS. However, drawbacks such as cost and turnaround time have prohibited the wide adoption of this testing for the diagnosis of PWS thus far. In the future, however, one or both assays may potentially replace other tests while addressing the heterogeneity of different genetic architectures causing PWS [37, 39].

Testing Algorithm

A flowchart summarizing the laboratory diagnostic pathway for investigation of suspected PWS is presented in Fig. 3.7. First-line molecular testing procedures should assess methylation of the PWS critical region, since methylation is abnormal in almost all true PWS cases. Abnormal methylation status confirms a diagnosis of PWS, but as mentioned previously, the underlying mechanism must be established to accurately guide management, genetic counseling, and recurrence risks. Thus, if methylation is assayed using a technique that does not evaluate 15q11.2q13 PWS critical region copy number, this should then be determined in all patients with methylation abnormalities. A comprehensive, definitive diagnosis requires a minimum of two tests, and depending on the choice of tests, these same two tests could exclude a structural chromosomal rearrangement [40]. Of importance, algorithms for clinical PWS testing are likely to evolve rapidly over the next several years as whole-exome sequencing and whole-genome sequencing become standard of care. Whereas many clinicians currently reflex to these assays in the case of negative results, eventually more streamlined approaches involving WES and/or WGS will likely emerge as standard of care [41].

Currently, MS-MLPA is the most common first-tier diagnostic test, as it simultaneously detects PWS critical region methylation status and copy number; however, other techniques (such as MS-PCR) are more sensitive in patients with low-level mosaicism. If deletion is detected using MS-MLPA, chromosome microarray anal-

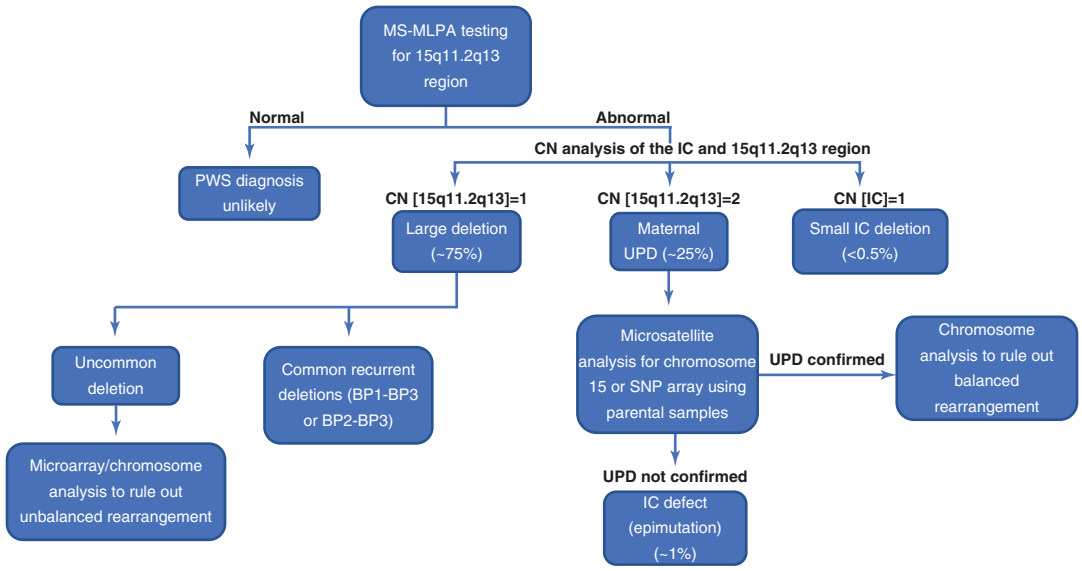

Fig. 3.7 Laboratory testing algorithm for molecular diagnosis of PWS

ysis should be considered to determine the nature and extent of the deletion, and karyotyping should be considered to identify possible chromosomal translocations. Testing can then be extended to other family members as appropriate. If abnormal methylation is detected without evidence of deletion, maternal UPD for chromosome 15 is the most likely explanation and should be confirmed using microsatellite analysis or SNP-based chromosome microarray analysis by performing a trio-analysis of the proband and both parents. In cases of full chromosome 15 heterodisomy, SNP-based chromosome microarray will be normal. In the absence of a deletion, if UPD for chromosome 15 is also ruled out, IC deletion or epimutation should be suspected.

Reporting Guidelines Following MS-MLPA

Normal result: Normal methylation and normal dosage of the 15q11q13 region. This result excludes paternal deletion, UPD, and IC defect. A diagnosis of PWS is highly unlikely. The sensitivity of the test should be mentioned on the report.

Abnormal methylation – deletion identified: Absence of paternal allele at the 15q11q13.2 region. This result confirms a diagnosis of PWS. Laboratories may recommend chromosome studies to exclude an unbalanced translocation involving chromosome 15.

Abnormal methylation – no deletion identified: Absence of a paternal allele at 15q11q13.2, normal dosage of the 15q11q13.2 region. This result confirms the diagnosis of PWS. The molecular cause of PWS may be either due to maternal UPD (most likely) or an IC defect (rare). Laboratories should recommend microsatellite studies on the family to help confirm or exclude UPD. Laboratories should also recommend chromosome studies to exclude a possible structural rearrangement (e.g., Robertsonian translocation).

Abnormal methylation – deletion of the imprinting center identified: Absence of paternal allele for SNRPN exon 1/intron 1 probes and possibly SNRPN u1B probe consistent with IC deletion. This result confirms the diagnosis of PWS. IC deletions are associated with a recurrence risk of up to 50%. In case of an IC deletion, the father should be investigated for the presence of the deletion since a familial IC deletion implies consequences for other family members.

Cost Considerations

When performing PWS testing, it is important to consider the cost of a test and turnaround times. In addition to many technical advantages and higher diagnostic yield of the MS-MLPA method, it offers a short turnaround time (3–5 days) and a lower cost (~US$250–350) compared with chromosome analysis (2–3 weeks; ~US$1000–1500), FISH (3–5 days; US$300–500), microarray (7–10 days; ~US$3600), and microsatellite (4–6 days, ~US$1500) analysis. The fewer the number of tests required, the more cost-effective the diagnosis becomes. Although a comprehensive diagnosis requires at least two tests, their choice may be limited by insurance approval, laboratory capabilities, turnaround times, and other factors that may need to be considered.

Prenatal Testing for PWS

As most PWS cases occur sporadically, there have been several studies focused on identifying the prenatal presentation of PWS. The most common ultrasound findings include intrauterine growth restriction and polyhydramnios (reviewed in [42]). Additionally, reduced fetal movement has been reported, likely related to the hypotonia observed in the perinatal period [42, 43]. Although these findings are not specific to PWS, when observed in combination methylation testing for PWS may be indicated. Since these findings are not specific to PWS, however, the majority of cases are identified by methodologies such as karyotype or chromosomal microarray and require follow-up testing by other methods.

In rare cases, there may be a familial abnormality that conveys significant recurrence risk. Chromosomal abnormalities, such as transloca-

tions involving chromosome 15, are one of the familial abnormalities that may be associated with a recurrence risk. Individuals who carry a translocation involving chromosome 15 (such as a Robertsonian translocation involving chromosome 15) have an increased risk of having a child with PWS. If a nondisjunction event involving chromosome 15 occurs in these individuals, the subsequent rescue mechanism may result in maternal UPD and therefore PWS. Rare cases of translocations involving chromosome 15 undergoing a similar rescue mechanism have been reported [44], although Robertsonian translocations are more common than unique translocations involving chromosome 15. Additionally, paternal IC mutations may also carry significant familial recurrence risks. In the context of a familial mutation leading to significant recurrence risk, genetic counseling is important, and preimplantation genetic testing or fetal testing may be of benefit.

In addition to potential ultrasound or familial reasons, there are certain prenatal testing results that should also raise concern for PWS. Most notably, if prenatal karyotype or microarray studies show evidence of mosaic trisomy 15 or a marker chromosome involving chromosome 15, these findings could be associated with an increased risk of PWS. Nonmosaic trisomy 15 is somewhat commonly observed in pregnancy losses; however, in some instances a trisomy rescue event can occur, resulting in the expected two copies of chromosome 15 [45]. If the trisomy was maternal in origin (the most common cause due to maternal meiosis nondisjunction), there would be a theoretical 1/3 risk of the resulting rescue being maternal uniparental disomy, and consistent with PWS [46–48]. The presence of a marker chromosome 15 could also suggest a partial trisomy rescue mechanism, also raising concern for resulting in maternal uniparental disomy and PWS.

When performing prenatal testing for PWS, as with any disorder associated with abnormal methylation, it is important to note that as an imprinting/methylation-related disorder, the tissue type being tested needs to be considered as imprinting may be incomplete during early embryonal development [49]. Specifically, when testing early pregnancies utilizing chorionic villus sampling (CVS), some of the markers historically used for PWS testing (PW71) do not show consistent results and should be avoided, whereas the SNRPN locus performs consistently on CV samples, as well as with amniotic fluid samples [21, 50].

With advances in maternal cell-free DNA (cfDNA) screening, which was originally utilized for screening of specific autosomal trisomies, there has naturally been a push toward utilization of this methodology to screen for subchromosomal abnormalities such as microdeletions. While this technology has not been widely used clinically to evaluate methylation status, and therefore is not relevant for screening for all causes of PWS, it has been attempted to be used for screening for the PWS deletion. This practice has been relatively successful when creating in silico reference material [51]; however, in practice, the overall performance of screening for the PWS deletion has been poor, with a very low positive predictive value (PPV) [52, 53]. Therefore, current prenatal screening guidelines do not recommend screening for this (or other microdeletions) using cfDNA [54]. In the context of a positive PWS deletion result, however, follow-up with diagnostic testing is necessary as the overall suspicion of a true positive is relatively low. Additionally, as this methodology does not test for all forms of PWS, cfDNA testing is not sufficient to rule out PWS, and clinical suspicion of PWS (e.g., due to ultrasound findings) should be followed by appropriate diagnostic testing.

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4 Monogenic and Syndromic Causes of Obesity

Jessica Duis and Merlin G. Butler

Introduction of Genetics of Obesity

Obesity is a significant health problem recognized worldwide. It is common in westernized societies including the United States where obesity has reached epidemic status, particularly during childhood where rates of obesity have doubled in the past 30 years. Obesity is a complex multifactorial disease involving genetic-environmental interactions. It is associated with excessive body fat that currently affects over one third of the world's population [1–5]. The World Health Organization defined body mass index (BMI) as a measure (i.e., kg/m^2) to determine overweight or obesity status. A BMI greater than 40 is defined as severe obesity [4, 6]. The prevalence of childhood obesity from 1990 to 2010 had increased from 4.2% to 6.7% and is expected to reach over 9% during the next decade with a corresponding increase in infertility [3]. Women in their mid-30s have a greater than 25% chance of being infertile when obese [7]. Other significant morbidities are associated with obesity including type II diabetes, hypertension, obstructive sleep apnea, cardiovascular diseases, cancers, depression, and increased mortality, thereby representing a serious public health problem worldwide.

A number of factors can contribute to obesity including a changing environment with more access to highly dense food sources, ingestion of increased calories, decreased physical activity in the general population secondary to a more sedentary lifestyle common in westernized societies, and advances in the workplace utilizing modern technology. These factors contribute to overall decreased energy expenditure. Influences of increased BMI also include inheritance of genetic risk factors in individuals with a family history of obesity with social, economic, and cultural circumstances [8–13].

Advances in genetic technology yield supporting evidence for identification of genes and their encoded proteins regulated by noncoding RNAs to provide a better understanding of the molecular mechanisms involved in body composition, regulation, and energy expenditure [14]. The group of genetic factors classified as monogenic is caused by mutations in single genes. Polygenic inheritance involves several genes or members of gene families and their interaction resulting in specific phenotypes. Abnormalities involving neurological developmental function or regulation of energy utilization, expenditure, or storage via hormone production, transport, or receptors impact overall energy homeostasis. Furthermore, heritability esti-

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mates indicate that genetic factors may contribute up to 70% of obesity using studies from monozygotic twins reared apart and living in different environments [15]. Heritability estimates increase from infancy through adolescence with longitudinal changes in BMI from adolescence to young adulthood that appear to be influenced by genetic traits and thereby contribute to obesity [16].

The focus of this chapter is to present evidence supporting monogenic causes of obesity involved in central or peripheral regulation of energy expenditure, caloric intake, and utilization of energy or physical activity with balance. Over 350 genes have been identified in the literature by searching keywords such as genes, genetic factors, and obesity and found to be clinically relevant, associated with or causative for obesity [17] (see Fig. 4.1). In addition, 21 of the 350 genes were also found to play a role in human reproduction or infertility. The obesity genes identified through this search primarily affect genetic pathways common in lipid metabolism, fat deposition or lipid transport, eating behavior, food selection and hormones, physical activity, or energy expenditure. Syndromic causes of obesity are also discussed as important considerations in the workup of obesity because these often offer insights into molecular pathways associated with obesity, as well as guide screening practices and anticipatory guidance in the context of management and treatment of patients.

Genetic Factors Contributing to Obesity

Monogenic Obesity

Research using genetic variants and analysis of genome-wide association studies (GWAS) since 2005 have identified informative gene loci for obesity by incorporating several hundred thousand DNA polymorphic markers or single-nucleotide polymorphisms (SNPs) distributed throughout the human genome. GWAS is a high-throughput method with the advantage to search for new genes without having previous evidence of the gene's role in specific disease causation. By the year 2010, at least 900 published GWAS associations were reported and 165 traits found or discovered in humans. Recruitment of large-scale case-control and population-based cohorts with both available DNA and clinical phenotypes is now available for study [18, 19]. The SNPs from obese and nonobese individuals when combined with statistical approaches have found a number of loci marking candidate genes to allow further testing and identification of their potential role in obesity [20]. A summary of obesity genes has been recorded in the literature during the past decade and included 176 single gene mutations in 11 different genes, 50 loci related to single gene (Mendelian) syndromes, 244 murine adiposity-related genes, 408 animal model based quantitative trait loci (QTLs), and 253 QTLs from 61 GWAS scans [21]. In 2007, using several approaches, investigators discovered DNA markers for one of these genes, *FTO* (fat mass and obesity associated), which is a major contributor for obesity in Europeans [22, 23], type 2 diabetes, and early-onset extreme obesity [24]. About 16% of adults studied were homozygous for a growing number of polymorphic DNA markers and risk alleles, specifically in individuals who weighed more by at least 3 kg and had a 1.7-fold increased risk of having obesity when compared with those without the specific risk alleles in this gene [22]. Furthermore, GWAS meta-analysis studies in the general population of European descendants supported the role of the FTO locus on BMI, along with multiple independent association signals reported for both *MC4R* and *BDNF* genes [25]. However, these loci explained only 1.45% of the variance in BMI suggesting that many other common genetic variants may impact BMI and are yet to be discovered. Interestingly, two gain of function coding polymorphisms of the *MC4R* gene (I251L and V103I) were negatively associated with obesity, and the V103I variant had a 20% lower risk for developing obesity in Europeans and a 31% reduction in Asians [26, 27]. In addition, the I251L variant for MC4R was reported to have a 50% lower risk for obesity in a meta-analysis study of European subjects [27].

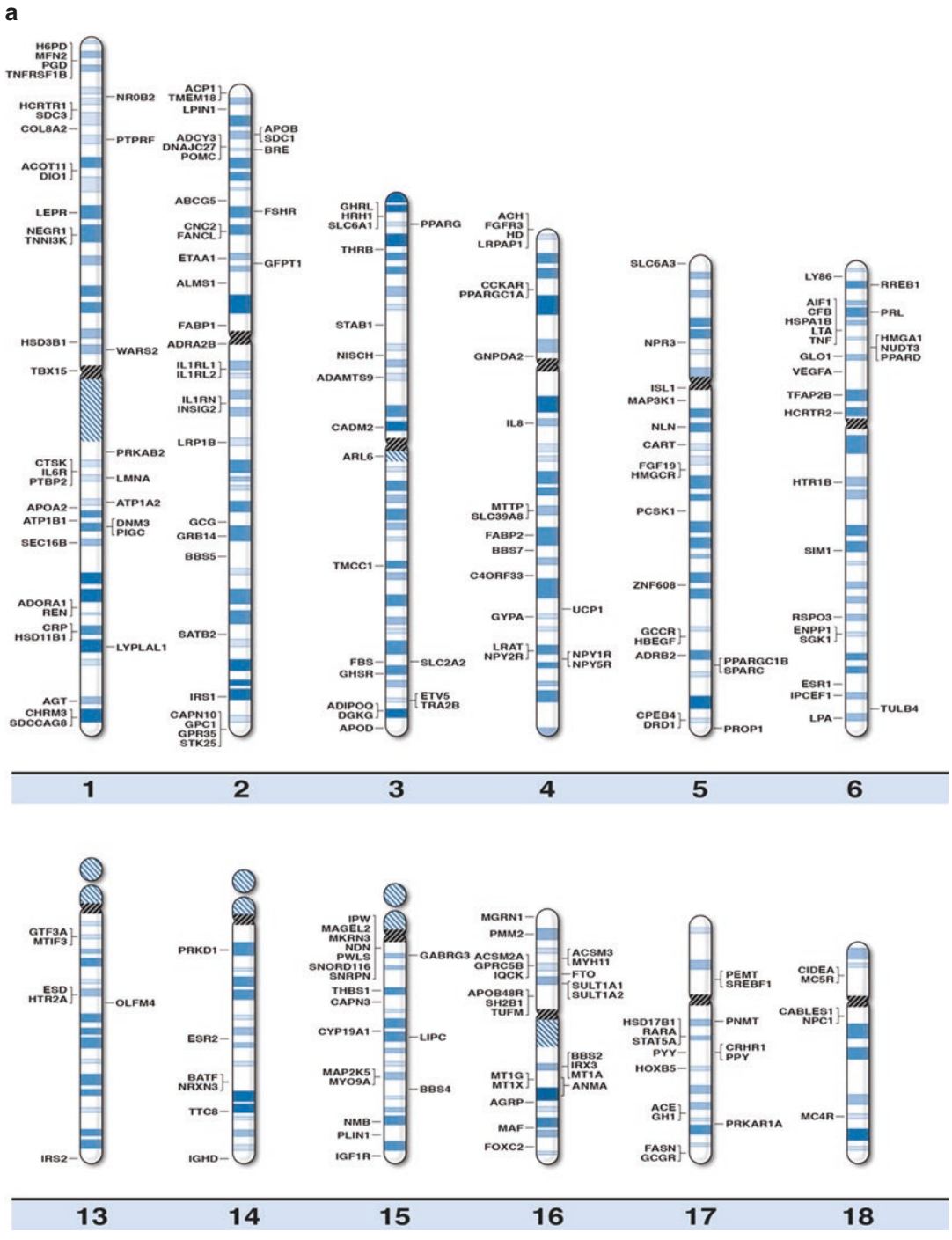


Fig. 4.1 (**a**) Obesity gene ideogram part A. High-resolution human chromosome ideograms (850 band level) with symbols representing recognized genes for obesity positioned at the chromosome band location. (**b**) Obesity gene ideogram part B. High-resolution human chromosome ideograms (850 band level) with symbols representing recognized genes for obesity positioned at the chromosome band location. (Published with permission from Butler et al. [17])

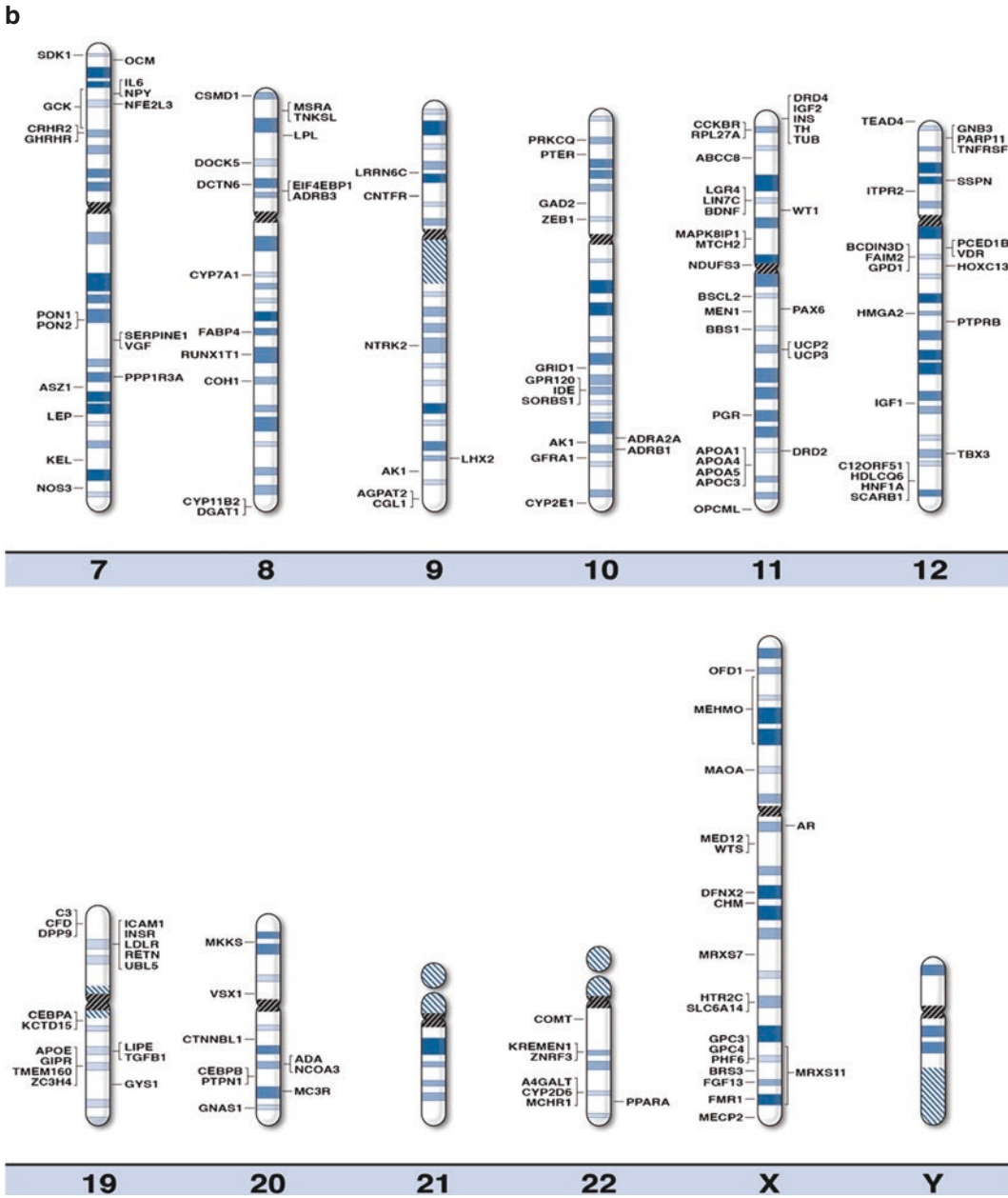


Fig. 4.1 (continued)

Evidence supporting SNPs impacting BMI in the adult population also applies to children. At least nine loci of five genes (*FTO*, *MC4R*, *TMEM18*, *MSRA*, and *NPC1*) are associated with extreme obesity with five loci influencing both BMI and waist circumference [24]. Four other loci hold a specific risk for extreme obesity including *MAF*, *PTER*, *PRL*, and *SDCCAG8* genes [20], while other examples of monogenic obesity factors include the leptin-melanocortin pathway involving *LEP*, *LEPR*, *SH2B1*, *POMC*, *PCSK1*, *MC4R*, and *MC3R* genes [10]. Abnormalities of these genes can result in monogenic forms of obesity including homozygous or heterozygous

compound mutation carriers or oligogenic forms of heterozygous gene carriers with great impact on the individual's obesity through their influence on food intake, energy expenditure, and nutrient balance. Other related genes encoding for ghrelin (*GHRL*) which encodes a peptide that stimulates eating at the brain level, and *PPARG* involved with metabolism, are both located on chromosome 3p25 [28].They play major roles in eating behavior and fat metabolism in humans. The *MC4R* is now recognized as the single most commonly associated gene causing childhood obesity and is found in about 4% of cases [29, 30]. The *MC4R*, *POMC*, and *GHRL* genes and their encoded proteins have been targets for clinical trials in treating hyperphagia and obesity and have met some success. Table 4.1 shows a list of genes, their chromosome location, and obesity phenotypes.

Additionally, the role of hormones in appetite and weight regulation in humans is becoming increasingly recognized and involves the central nervous system (CNS), particularly regions in the hypothalamus. The fundamental role in appetite regulation and energy balance is in response to changes in peripheral circulating signals, neuroendocrine peptides, hormones, and nutritional factors. These signals impact the CNS, specifically the arcuate nucleus, where they are received and integrated in two distinct neuron populations involving the agouti-related protein (AgRP) and regulation of satiety and/or pro-opiomelanocortin (POMC) for feeding. These neurons help energy balance and homeostasis by sensing and integrating various metabolic signals through their activity or processes observed in the hypothalamus, for example, leptin, a peptide generated peripherally by fat cells binding to receptors in the brain that triggers signaling pathways that ultimately activates POMC-related neurons. In connection with NPY/AgRP/GABA neurons inhibition, leptin exerts an anorexigenic effect or decreased eating behavior in humans. Conversely, a second neuroendocrine peptide (ghrelin) produced by the stomach binds to its CNS receptor, the growth hormone receptor (GHR), which induces activation of the AgRP-related neurons, inhibits the POMC neurons in the arcuate nucleus, and exerts an orexigenic or increased eating effect [32–34].

Table 4.1 Genes and their relationship to obesity, phenotypes, chromosome location, and as candidates for obesity

Obesity and Classification
Generalized: 1p35.2 (*SDC3*), 3p25.3 (*GHRL*), 4q31.1 (*UCP1*), 5q13.2 (*CART*), 5q32 (*ADRB2*; *PPARGC1B*), 6q23.2 (*ENPP1*), 8p11.23 (*ADRB3*), 13q14 (*OLFM4*), 14q32.2 (*MEG-DMR*), 16p11.2 (*SH2B1*), 16q22.1 (*AGRP*), 6p12.3 (*TFAP2B*), 17q21 (*HOXB5*), 17q21.31 (*PYY*), 4q31.21 (*IL15*), 4q22.1 (*NAP1L5*), 6p25.1 (*LY86*), 10q11.22 (*PPYR1*), 2p25.3 (*TMEM18*), 20q11.23 (*CTNNBL1*), 19q13.11 (*KCTD15*), 11p11.2 (*MTCH2*), 8p11.23 (*ADRB3*), 9q21.33 (*TRKB*), 11q13.2 (*PC*), 14q24.3–q31.1 (*NRXN3*), 11p15.4 (*TUB*)
Early onset: 1p36.11 (*NROB2*), 2p23.3 (*POMC*), 18q21.32 (*MC4R*), Xq27.3 (*FMR1*), 16q12.2 (*FTO*), 11p14.1 (*BDNF*)
Severe: 3p25.2 (*PPARG*), 6q16.3 (*SIM1*), 11q13.4 (*ULP3*), 16p11.2 (*SH2B1*), 7q32.1 (*LEP*), 1p31.3 (*LEPR*), 5q15 (*PCSK1*), 9q21.33 (*NTRK2*), 4p14 (*TBC1D1*), 1p31.1 (*NEGR1*), 18q11.2 (*NPC1*), 16q23.2 (*MAF*), 10p13 (*PTER*), 6p22.3 (*PRL*), 8p23.1 (*TNKS*), 2p25.3 (*TMEM18*), 8p23.1 (*MSRA*), 3q29 (*CEP19*), 2q14.1–q14.2 (*INSIG2*)
Description of Genetic Evidence and Obesity Phenotypes
Proposed genetic loci associated with child and/or adult BMI levels including extreme obesity identified by genome-wide studies (*GWAS*), linkage analysis, exome sequencing, and/or with CNV/SNP microarrays
Other genes of interest in obesity: *TMEM18, GNPDA2, INSIG2, KCTD15, CTNNBL1, MTCH2, NPC1, FAIM2, TFAP2B, SEC16B, ETV5, AIF1, GPRC5BB, MAP2K5, GIPR, FANCL, SDCCAG8, GHRL, MC3R, TNKS-MSRA, TNN13K, LRRN6C, FLJ35779, SLC39A8, TMEM160, CADM2, LRP1B, PRKD1, MTIF3, ZNF608, PTBP2, HMGA1, PPYR1*
Genes associated with childhood obesity: novel loci: *SH2B1, EDIL3, S1PR5, FOXP2, TBCA, ABCB5, ZPLD1; KIF2B, ARL15, ENPP1, SDCCAG8, TNK*
Genes associated with childhood and/or adult waist to hip ratio development: *LYPLAL1, C12orf51, LY86; HOXC13, RSPO3, VEGFA, TBX15, NFE2L3, GRB14, DNM3, PIGC, ITPR2, ADAMTS9, ZNRF3, NISCH, CYEB4*

Adapted from Butler [31]

POMC plays a fundamental role in the leptin-melanocortin system with a deficiency causing absence of ACTH and alpha-MSH, which are cleavage products from POMC protein and involved in both appetite and pigment production. Therefore, POMC deficiency can lead to hyperphagia, severe obesity, and red hair [35, 36]. Leptin is produced by fat cells and is one

of the major components of the peripheral and CNS connection in the regulation of body weight and fat mass accumulation in humans [37, 38]. Therefore, disturbances in CNS hypothalamic pathways involving peripheral signaling can lead to appetite dysregulation as well as excessive weight gain and increased appetite (orexigenic) or weight loss with decreased appetite (anorexogenic). It is estimated that over 30 neuroendocrine peptides exist that play a role in the CNS and peripheral signaling of appetite regulation and when disturbed can cause obesity. Variants or defects of genes causing both syndromic or non-syndromic obesity may involve both dysregulation of neuroendocrine peptide production and errors in cleavage of a master protein such as POMC, which requires prohormone convertase (PC1) to break POMC into smaller but functional peptides [39, 40]. If errors occur in peptide formation and their interaction with CNS pathways for appetite control, then obesity can result. Examples of monogenic, polygenic, and syndromic causes of obesity will be described and illustrated in this chapter.

Chromosome Anomalies and Obesity

Advances in genetic technology have allowed for reliable detection of structural, chromosomal, and DNA abnormalities causing both rare and common forms of obesity. For example, chromosome deletions and duplications have been found in syndromic obesity and summarized by Dasouki et al. [41]. Examples of chromosome defects with obesity as a manifestation with or without syndromic classification include 1p36 deletion, 2q37.3 deletion, 3p23 duplication, 3p25.3 duplication (contains *GHRL* gene), 4q32.1 duplication, 4q35.1 duplication, 5p13.1 duplication, 6q16.2 deletion (contains *SIM1* gene), 6q22.2 deletion, 6q24.3 duplication, 6q15–q21 deletion (contains *SIM1* gene), 6q16–q21 deletion (contains *SIM1* gene), 6q16.1–q16.3 deletion (contains *SIM1* gene), 7q36 deletion, 9p23 deletion, 9q34 deletion, 9q34.3 deletion, 9q33.3q34 duplication, 10q22.3q23.2 duplication, 11p12–p14 deletion, 11p13–p14.2 deletion (contains *BDNF* gene); 11p11.2 deletion, 12p13.1 duplication, 12qter deletion, 14q32.2 hypomethylation status (involves maternal disomy 14), 16q13 duplication, 16p11.2 deletion (contains *SH2B1* gene), 16q11.2–q13 duplication (contains *FTO* gene), 18q12.2–q21.1 deletion, 19q12–q13.2 duplication, 19q13.2 deletion, 20q13.13–q13.32 deletion, 22q11.2 deletion, Xq26.3–q27.3 deletion (contains *FMR1* gene), Xq23q25 duplication, Xp11.3p21.1 duplication, Xp11.4q11.2 inversion, and Xq27.1–q28 deletion (contains *FMR1* gene). Small deletions involving the chromosome 16p11.2 band which includes *SH2B1* gene have been reported in 0.5–0.7% of individuals with severe obesity and not found in nonobese healthy individuals. The *SH2B1* gene is also an obesity-related gene that impacts leptin sensitivity and therefore caloric intake and obesity in humans. Chromosome microarray studies have shown rare CNVs that are larger than 2 Mb in size and found in 1.3% of obese individuals with consistent disruption of multiple candidate genes for obesity (e.g., *POMC*, *UCP1*, *GHRL*, *FTO*, *SIM1*, *BDNF*, *FMR1*). Additionally, Butler et al. [17] summarized peer-reviewed reports from the literature and authoritative computer websites and found 370 clinically relevant and known genes reported in association with obesity that were then plotted on chromosome ideograms to represent a visual display of gene location and distribution (see Fig. 4.1a, b).

Several genes associated with obesity with additional clinical features involve pathways leading to hypogonadotropic hypogonadism, hypotension, behavioral problems, multiple affected organ systems, and possibly seizures [42]. For example, the leptin receptor, leptin, UCP1, or POMC deficiencies are key players in single gene causes of obesity [43–45]. Polygenic causes of obesity with recognized mutations include *MC4R*, *FTO*, and *INSIG2* genes [46–48]. Classical obesity-related syndromes with key features of marked obesity include Prader-Willi, Alstrom, Bardet-Biedl, fragile X, Albright hereditary osteodystrophy, and Smith-Magenis syndromes or related chromosome defects such as microdeletion disorders (e.g., 16p13) [31]. Historically, about 30 syndromes associated with obesity have been reported along with several dozen chromosomal defects, but Kaur et al. [19] found evidence for

79 obesity syndromes described in the medical literature. Of these 79 obesity syndromes, 19 were fully elucidated or characterized genetically, 11 were partially characterized, and 27 had been genetically mapped to a chromosome region, but not well characterized. The remaining 22 had not been mapped to a chromosome location nor has a causative gene(s) identified. Clinical features among the 79 identified obesity syndromes often overlap; for example, at least 52 syndromes displayed some form of intellectual disability, while 7 syndromes presented with macrocephaly and 7 syndromes with microcephaly.

Syndromic Obesity Associated with Chromosomal Anomalies

1p36 Deletion Syndrome 1p36.33-pter deletion of ~139 Mb in size is associated with psychomotor delay, developmental delay in particular impacting expressive language, hypotonia, and craniofacial dysmorphism. It is associated with a Prader-Willi syndrome-like phenotype including hyperphagia. Features also include self-injurious behaviors, seizures, congenital heart disease, and hypothyroidism. Some patients exhibit intrauterine growth delay and microcephaly. In those patients exhibiting excessive weight gain, increasing weight is noted after 2 years of life [49].

3p25.3p26.2 Duplication Syndrome A 3p25.3p26.2 duplication was reported by Bittel et al. [28] in a 9-year-old male presenting with features of Prader-Willi syndrome including a mild pervasive developmental disorder and learning impairment. He had central obesity with onset occurring rapidly at 4 years of age despite food restriction. He had a relatively small penis and poorly rugated scrotum with descended testicles. He had tapering digits with a round appearing face with full cheeks (Fig. 4.2). He was 1 year behind his peers in the school setting requiring occupational, speech, and behavioral therapies with special attention for reading and math. Fragile X DNA testing and PWS methylation analyses were normal, but routine chromosome studies showed a chromosome 3p25.3p26.2 duplication supported by comparative genomic hybridization. The 3p segment contains genes which contribute to obesity and behavior, most notably ghrelin (*GHRL*), oxytocin receptor (*OXTR*), solute carriers for GABA neurotransmitter (*SLC6A1* and *SLC6A11*), and peroxisome proliferator-activated receptor (*PPARG*). RT-PCR gene studies were undertaken and suggested disturbed (increased) expression of the genes.

Fig. 4.2 Frontal view of a 9-year-old male with a duplication of chromosome 3p25.3p26.2. Reproduced with permission by Bittel et al. [28]. https://pubmed.ncbi.nlm.nih.gov/16470700/

5p13 Microdeletion Syndrome (Trisomy 5p) Recurrent microduplications of 5p13.1–p13.2 of ~3.7 Mb in size are most often de novo, although there is one case report of an affected family in which the duplication was located on

the short arm of the X chromosome [50]. It is often due to a complex rearrangement involving other chromosomes, and this should be considered when a diagnosis is suspected. Variability is associated with the size and location of the duplication. It appears to have a predilection for males. Features include hypotonia, developmental delay, autism spectrum disorder, hypertension, macrocephaly, arachnodactyly, and characteristic facial features. It is thought to be associated with increased dosage of *NIPBL*. Heart defects and seizures should be ruled out. Weight gain and obesity often develop in older individuals. Lymphedema may be secondary to obesity or an independent feature.

6q16 Deletion Deletions reported to date are in the 6q16.1–q16.2 region of approximately 4.1 Mb in size. Patients exhibit a Prader-Willi-like clinical phenotype including hypotonia, developmental delay, autistic-like behavior, obesity, and short hands and feet. All cases have been associated with a chromosomal rearrangement by karyotype analysis. Other features may include congenital heart disease. The candidate gene in the region associated with obesity is the *SIM1* gene. The *MCHR2* gene is also in the region and thought to be involved in feeding behavior and metabolism [51].

16p11.2 Deletion Syndrome A recurrent heterozygous deletion of ~593 kb in size on chromosome 16 is characterized by developmental delay including motor and language with expressive communication and cognition and intellectual disability with susceptibility to autism spectrum disorders. It may be inherited from an unaffected parent that may be identified at the time of the diagnosis of the child. Up to 20% of patients develop seizures. Brain anomalies are reported including Chiari malformations/cerebellar ectopia. Care should be taken to rule out other congenital anomalies, in particular, vertebral anomalies. Obesity typically starts in adolescence in affected individuals [52].

Down Syndrome Down syndrome is most often caused by a nondisjunction event, in which the individual inherits three copies of chromosome 21. It is associated with distinct facial features, hypotonia, developmental delay, intellectual disability, congenital heart disease, gastrointestinal issues, myelodysplasia, increased risk of infection, endocrinopathies, and eye concerns. Individuals with trisomy 21 develop obesity in childhood and adolescence. Obesity is associated with obstructive sleep apnea, dyslipidemia, hyperinsulinemia, and gait concerns [53].

Turner Syndrome Turner syndrome (TS) is caused by monosomy X. Characteristics include short stature responsive to growth hormone, streak gonads resulting in amenorrhea, and lack of secondary sex characteristics requiring treatment with hormone replacement therapy. In addition, the female patients may have heart defects, edema, and distinctive dysmorphic features. Individuals with TS have an increased risk of autoimmune disorders, overweight and obesity, and metabolic disorders including insulin resistance and dyslipidemia. This risk increases from childhood to early adulthood [54].

Klinefelter Syndrome Klinefelter syndrome is caused by 47,XXY. The primary feature is infertility and atrophic testes that may not be identified until fertility is desired. Other features include social challenges and a tall and lanky stature. Hypogonadism causes an unfavorable change in body composition and truncal obesity [55].

Syndromic Obesity

In addition to early-onset morbid obesity, a wide breadth of clinical features should prompt the clinician to consider syndromes or multiple clinical features associated with one specific genetic cause. The importance of early identification of the specific syndrome or genetic cause of obesity may change management and provide insight into regular screening of other organ systems for complications or offer targeted therapies. A list of syndromes associated with obesity is found in Table 4.2 along with involved gene(s),

Table 4.2 List of obesity-related syndromes with genetic and clinical features

Disorder	Gene(s)	Inheritance pattern	Clinical features	Obesity features	References
Alstrom syndrome	*ALMS1*	Autosomal recessive	Cone-rod dystrophy, obesity, progressive bilateral sensorineural hearing impairment, acute infantile-onset cardiomyopathy and/or adolescent- or adult-onset restrictive cardiomyopathy, insulin resistance/type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease (NAFLD), and chronic progressive kidney disease	Truncal obesity developed during the first year of life	Paisey et al. [56] Marshall et al. [57]
Bardet-Biedl syndrome	*BBS1*, *BBS2*, *BBS4*, *BBS5*, *BBS7*, *BBS9*, *TTC8* (BBS8), *ARL6* (BBS3), *BBS10*, *BBS12*, *MKKS* (BBS6), *C8orf37* (BBS21), *CEP164*, *CEP290* (BBS14), *IFT27* (BBS19), *IFT74* (BBS20), *IFT172* (BBS20), *LZTFL1* (BBS17), *MKS1* (BBS13), *SCAPER*, *SCLT1*, *SDCCAG8* (BBS16), *TRIM32* (BBS11), *WDPCP* (BBS15)	Autosomal recessive oligogenic inheritance in families with variants in 2 or more BBS associated genes	Retinal cone-rod dystrophy, eye anomalies, obesity and related complications, postaxial polydactyly, cognitive impairment, seizures, hypertonia, ataxia/poor coordination, hypogonadotropic hypogonadism and/or genitourinary malformations, hearing loss, anosmia, oral/dental anomalies, behavioral concerns, and renal malformations and/or renal parenchymal disease	Central obesity develops in the first year of life	Forsyth and Gunay-Aygun [58]
Borjeson-Forssman-Lehmann syndrome	*PHF6*	X-linked	Developmental delay, intellectual disability, obesity, seizures, swelling of the subcutaneous tissues of the face, skeletal anomalies, large ears, failure of the testes in males or the ovaries in females to produce hormones (hypogonadism), gynecomastia, and distinctive facial features	Obesity is common in affected children even during infancy	Lower et al. [59] Bellad et al. [60]
Carpenter syndrome	*RAB23*	Autosomal recessive	Peculiar facies with brachycephaly due to early fusion of the coronal, sagittal, and lambdoidal sutures, polydactyly, brachymesophalangy, mild soft tissue syndactyly, obesity, hypogenitalism, congenital heart disease, and intellectual disability	Mild to moderate obesity of the face, neck, trunk, forearms, and thighs	Hidestrand et al. [61]
CHOPS syndrome	*AFF4*	Autosomal dominant	Cognitive impairment, coarse facial features, heart defects, obesity, pulmonary problems, short stature, skeletal anomalies; features overlap with Cornelia de Lange syndrome	All reported individuals are obese	Raible et al. [62]

(continued)

Table 4.2 (continued)

Disorder	Gene(s)	Inheritance pattern	Clinical features	Obesity features	References
Chudley-Lowry syndrome	*ATRX*	X-linked	Moderate to severe mental retardation, short stature, mild obesity, hypogonadism, and distinctive facial features characterized by depressed nasal bridge, anteverted nares, inverted V-shaped upper lip, and macrostomia	Mild obesity	Abidi et al. [63]
Coffin-Lowry syndrome	*RPS6KA3*	X-linked	Severe to profound intellectual disability in males, short and soft fleshy hands with tapered fingers, progressive kyphoscoliosis with neuropsychiatric concerns including behavioral problems, loss of strength, progressive spasticity or paraplegia, sleep apnea, or stroke. Stimulus-induced drop attacks (SIDAs) in which unexpected tactile or auditory stimuli or excitement triggers a brief collapse	Obesity may be present	Rogers et al. [64]
Cohen syndrome	*VPS13B*	Autosomal recessive	Failure to thrive in infancy and childhood; truncal obesity in the teen years; early-onset hypotonia and developmental delays; microcephaly developing during the first year of life; moderate to profound psychomotor retardation; progressive retinochoroidal dystrophy and high myopia; neutropenia in many with recurrent infections and aphthous ulcers in some; a cheerful disposition; joint hypermobility; and characteristic facial features with prominent central incisors	Truncal obesity appearing in or after mid-childhood	Wang et al. [65]
Cornelia de Lange syndrome	*NIPBL*, *RAD21*, *SMC3*, or *BRD4*, or a hemizygous pathogenic variant of *HDAC8* or *SMC1A*	Autosomal dominant, X-linked	Distinctive facial features, growth restriction (prenatal onset), hypertrichosis, upper-limb reduction defects, broad IQ range (30–102), autistic features, self-destructive tendencies, GI dysfunction, congenital heart disease, hearing loss, myopia, genital anomalies	Tendency to overweight/frank obesity	Deardorff et al. [66] Mariani et al. [67]
Disorders of GNAS Inactivation	*GNAS*	Autosomal dominant	Pseudohypoparathyroidism Ia, and Ic: end-organ resistance to hormones including PTH, TSH, LH, FSH, GHRH, developmental delay, variable intellectual disability and obesity Albright hereditary osteodystrophy: short stature, round facies, subcutaneous ossifications, and brachydactyly (shortening of the fourth and/or fifth metacarpal and metatarsals and distal phalanx of the thumb)		Haldeman-Englert et al. [68] Butler [69]

Fragile X syndrome	CGG trinucleotide repeat expansion in the 5' UTR of *FMR1*	X-linked	Intellectual disability, autism spectrum disorder, behavioral concerns, hypotonia, gastroesophageal reflux, seizures, sleep disturbances, joint laxity, pes planus, scoliosis, macro-orchidism, recurrent otitis media, large ears, mild dysmorphic features [10% with Prader-Willi phenotype (PWP)]	Obesity and excessive appetite	Hunter et al. [70] McLennan et al. [71]
Growth hormone receptor deficiency	*GHR*	Autosomal recessive	Short stature, reduced muscle strength and endurance, obesity, hypoglycemia in infancy, small genitals, delayed puberty, thin and fragile hair and dental abnormalities		Baumbach et al. [72]
Kabuki syndrome	*KMT2D, KDM6A*	Autosomal dominant, X-linked	Typical facial features, minor skeletal anomalies, persistence of fetal fingertip pads, mild-to-moderate intellectual disability, congenital heart disease, GU anomalies, cleft lip and/or palate, GI problems, eye anomalies, widely spaced teeth and hypodontia, increased risk of infections and autoimmune disorders, seizure, endocrine anomalies, feeding problems, hearing loss, and postnatal growth deficiency	Adolescents and adults may have obesity	Adam et al. [73]
Kallmann syndrome	*KAL1*, *FGFR1*, *FGF8*, *PROKR2*, *PROK2*	X-linked recessive, autosomal recessive, autosomal dominant with incomplete penetrance, and most probably digenic/ oligogenic inheritance	Hypogonadotropic hypogonadism with anosmia	Obesity reported in *PROKR2* and *KAL1* gene variants	Dodé et al. [74] Dodé and Hardelin [75]
Kleefstra syndrome	*EHMT1*, 9q34.3 deletion	Autosomal dominant	Intellectual disability, psychiatric and autistic-like features, childhood hypotonia, congenital heart defects, genital anomalies, severe respiratory infections, seizures, and distinctive facial features	Weight increases in childhood leading to obesity	Kleefstra and de Leeuw [76] Williemsen et al. [77]
MOMO/ MORM	Unknown *INPP5E*	Unknown Autosomal recessive	Macrocephaly, obesity, mental (intellectual) disability, and ocular abnormalities (MOMO) Moderate learning problems, truncal obesity, a congenital nonprogressive retinal dystrophy, and micropenis in males (MORD)	Truncal obesity	Di Donato et al. [78] Hampshire et al. 2006 [79]

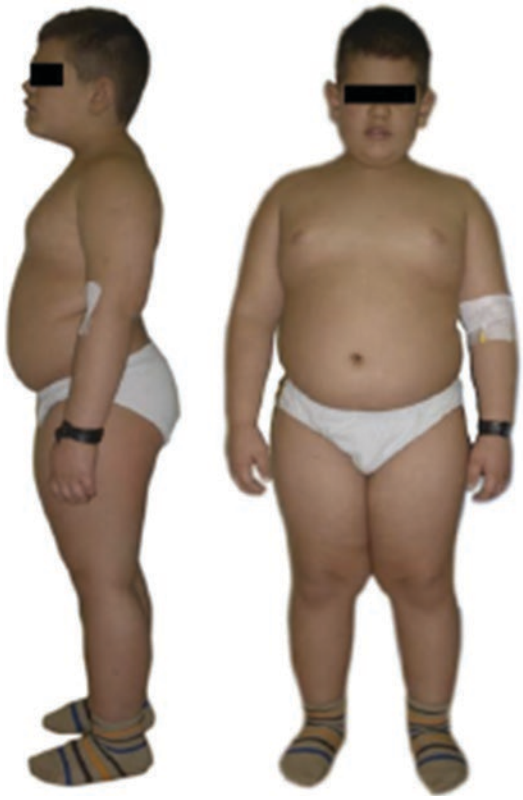
(continued)

Table 4.2 (continued)

Disorder	Gene(s)	Inheritance pattern	Clinical features	Obesity features	References
Prader-Willi syndrome	Lack of imprinted paternally expressed genes in chromosome 15q11.2–q13 region, most often due to a deletion *SNRPN*	Autosomal dominant (most often sporadic)	Severe hypotonia, poor suck, developmental delay and intellectual disability, hypogonadism/hypogenitalism, hyperphagia and childhood onset of obesity, small hands and feet, characteristic behavior (e.g., skin picking, outbursts, anxiety), endocrinopathies with mild dysmorphic features	Hyperphagia develops around age 8 years with development of obesity, if environmental controls are not in place	Butler [31] Angulo et al. [80] Driscoll et al. [81] Butler et al. [82]
Rubinstein-Taybi syndrome	*CREBBP*, *EP300*	Autosomal dominant	Distinctive facial features, broad and often angulated thumbs and halluces, short stature, and moderate-to-severe intellectual disability	Obesity may develop in childhood or adolescence	Stevens [83]
Smith-Magenis syndrome	Deletion 17p11.2 *RAI1*	Autosomal dominant (most often sporadic)	Distinctive physical features, feeding difficulties, hypotonia, developmental delay, sleep disturbances, maladaptive and self-injurious behaviors, cognitive impairment, behavioral abnormalities, sleep disturbance, and childhood-onset abdominal obesity	Childhood-onset truncal obesity	Smith et al. [84]
WAGRO	BDNF	Autosomal dominant	Wilms tumor, aniridia, genitourinary anomalies, intellectual disability, and obesity (WAGRO)	Childhood onset obesity	Rodríguez-López et al. [85]
Temple syndrome	Aberrations at the 14q32.2 imprinted region/maternal disomy 14	NA	Pre-and postnatal growth delay, feeding difficulties, hypotonia, motor developmental delay (with or without mild intellectual disability) and mild facial dysmorphism, premature puberty, and variable bone abnormalities	Childhood-onset central obesity	Kagami et al. [86] Butler [69]

inheritance pattern, clinical description, and reference citations. A collection of images is found below representing individuals with syndromic obesity conditions.

Alstrom Syndrome



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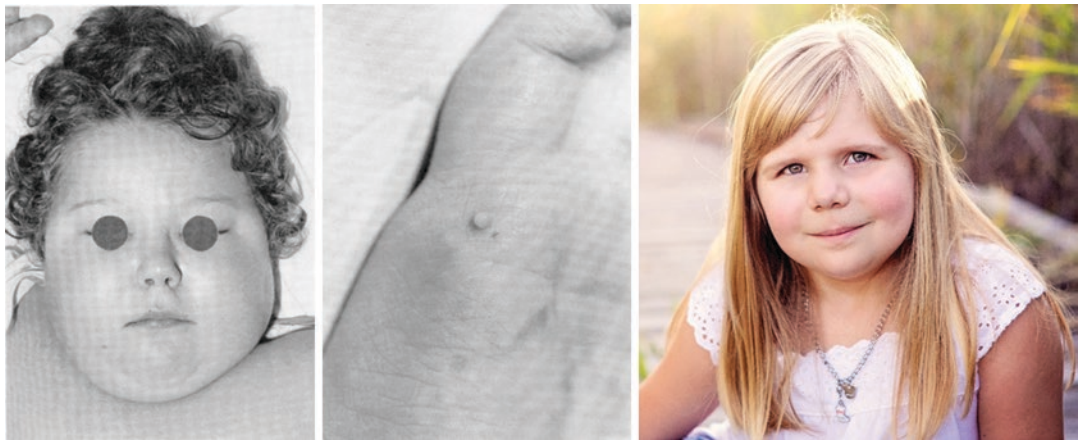
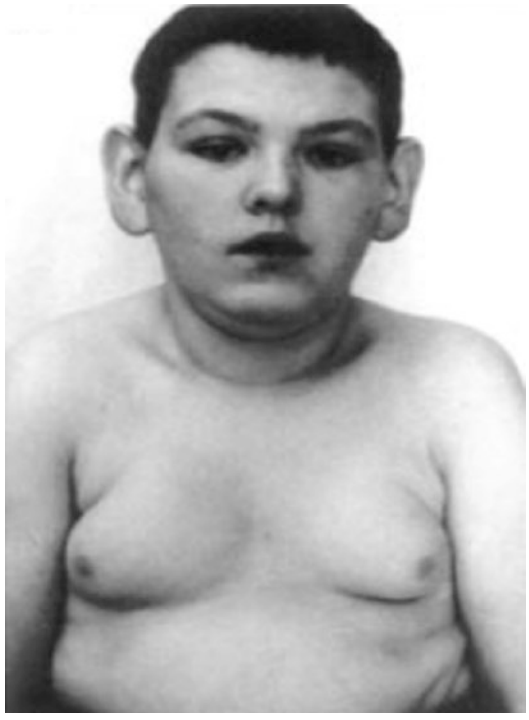
Bardet-Biedl Syndrome



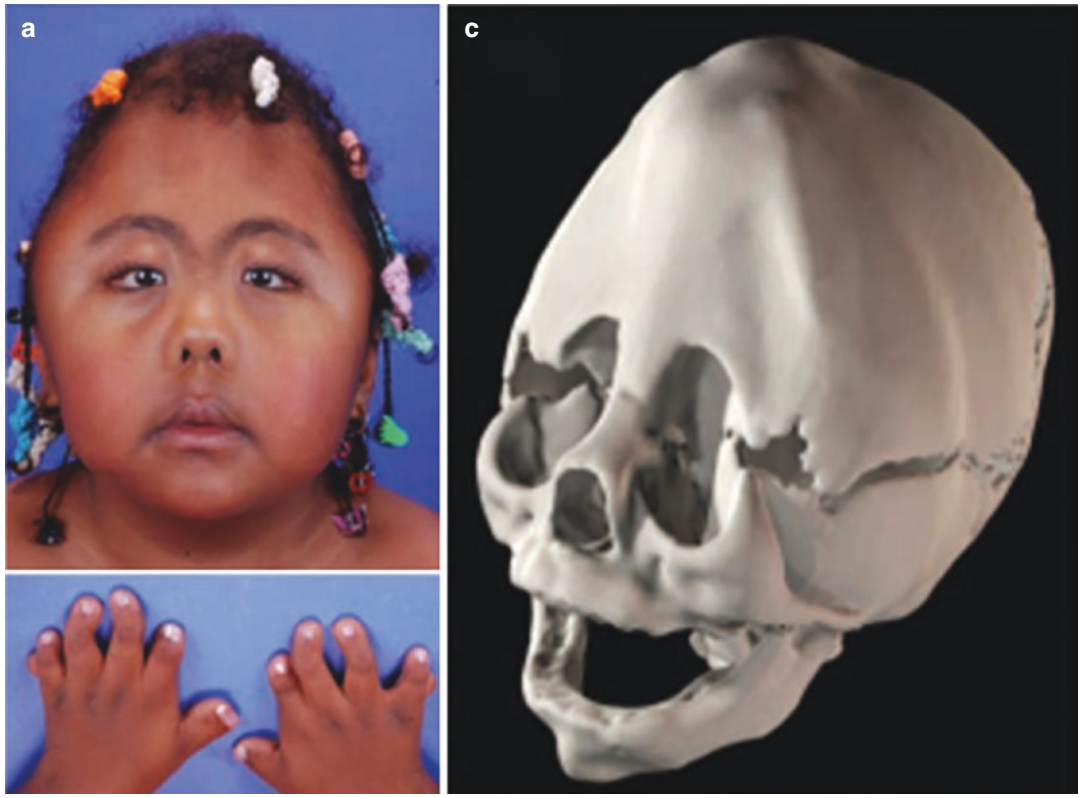
Reproduced with permission by Barakat et al. [87]. Image on far right used with patient family permission. https://pubmed.ncbi.nlm.nih.gov/2253248/

Borjeson-Forssman-Lehmann Syndrome



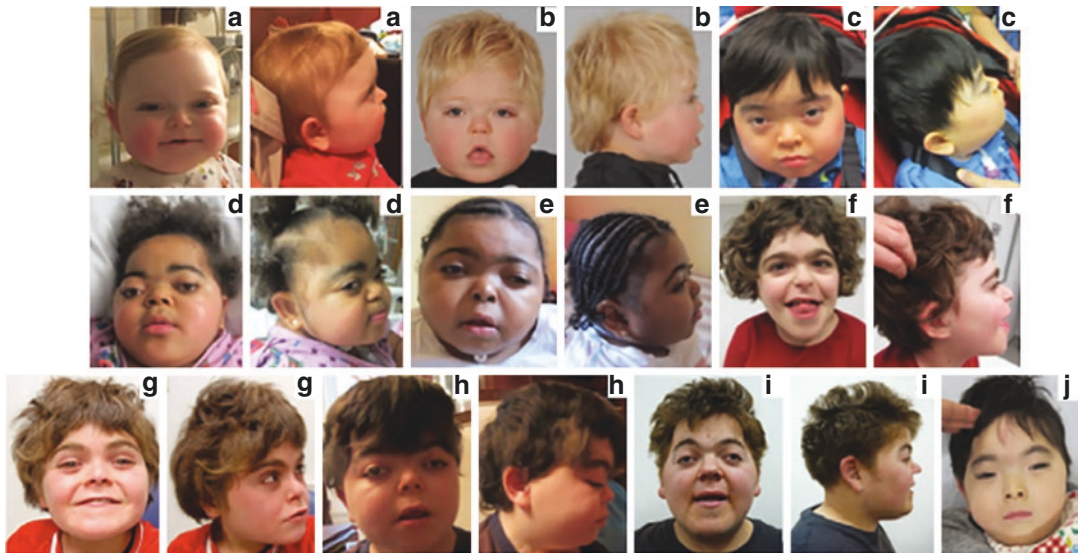
Reproduced with permission by Baumstark et al. [88]. https://pubmed.ncbi.nlm.nih.gov/12676923/

Carpenter Syndrome



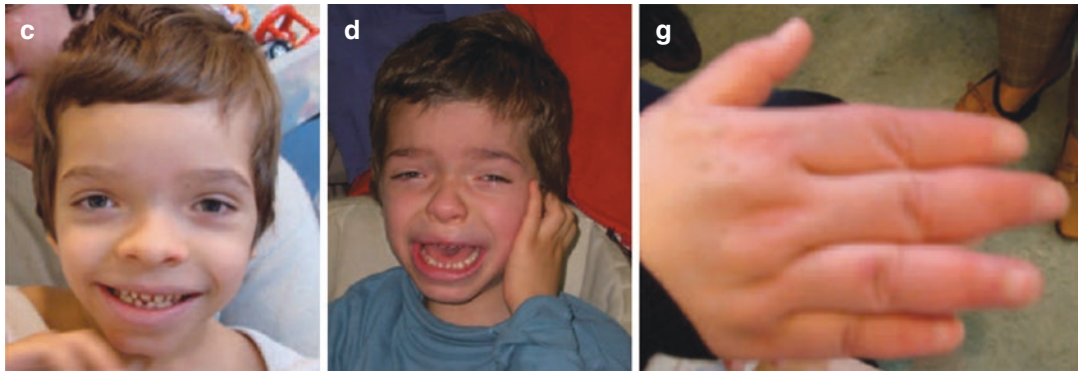
Reproduced with permission by Jenkins et al. [89]. https://pubmed.ncbi.nlm.nih.gov/17503333/

CHOPS Syndrome



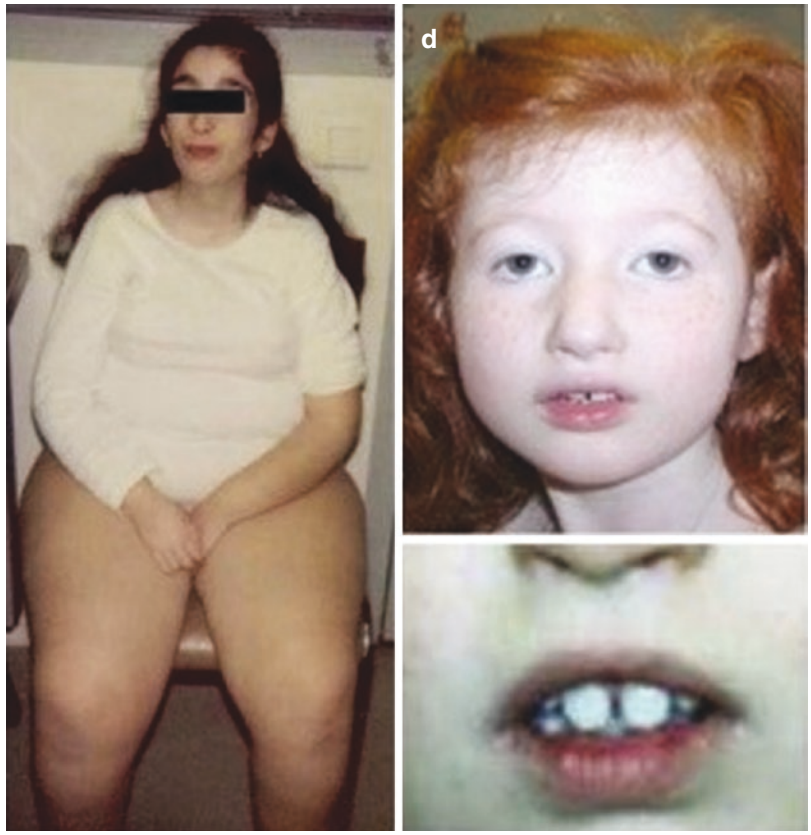
Reproduced with permission by Raible et al. [62]. https://pubmed.ncbi.nlm.nih.gov/31058441/

Coffin-Lowry Syndrome



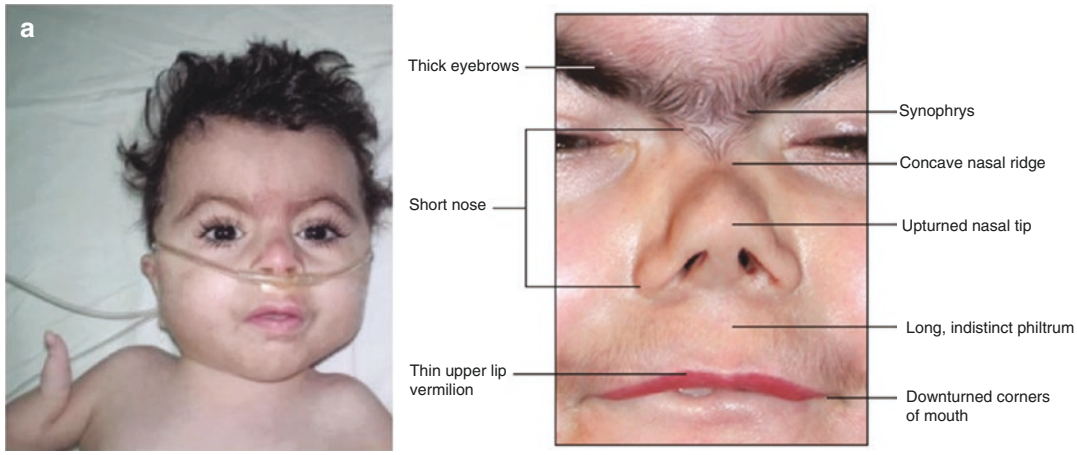
Reproduced with permission by Pereira et al. [90]. https://pubmed.ncbi.nlm.nih.gov/19888300/

Cohen Syndrome



Reproduced with permission by El Chehadeh-Djebbar et al. [91]. https://pubmed.ncbi.nlm.nih.gov/23188044/

Cornelia de Lange Syndrome



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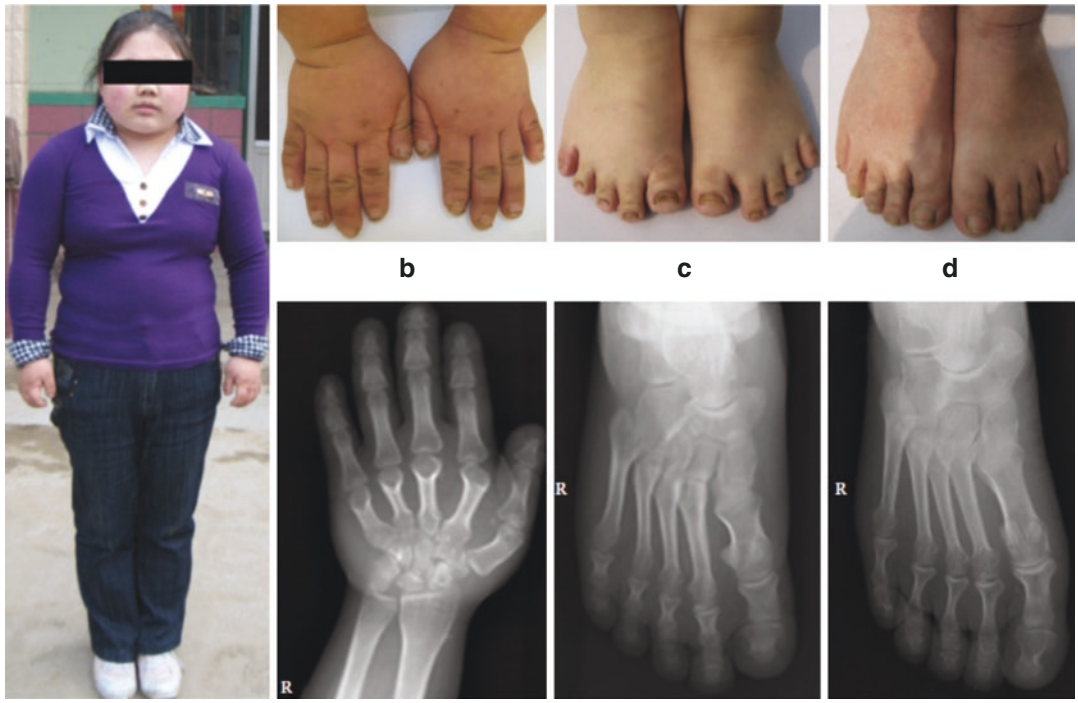
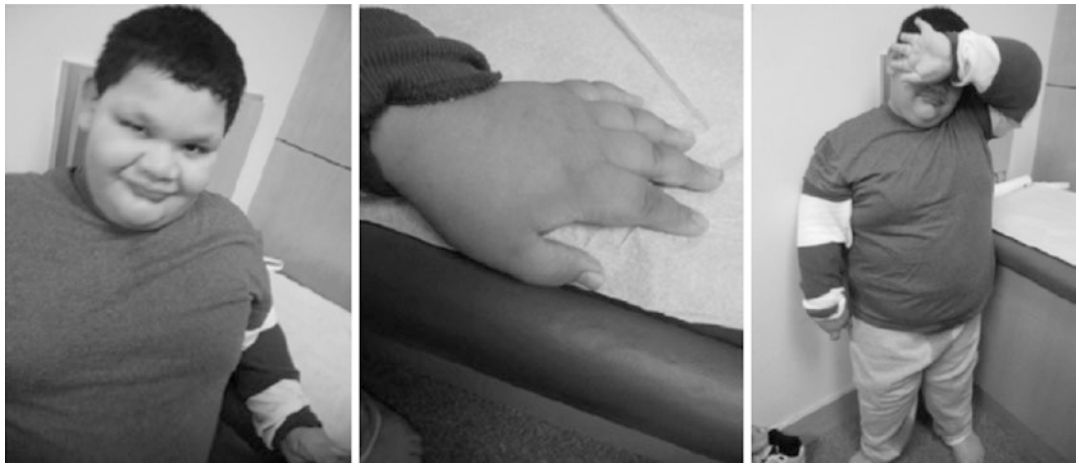
Disorders of GNAS Inactivation



Reproduced with permission by Miao et al. [93]. https://pubmed.ncbi.nlm.nih.gov/21822432

Fragile X Syndrome



Reproduced with permission by McLennan et al. [71]. https://pubmed.ncbi.nlm.nih.gov/22043169/

Kabuki Syndrome

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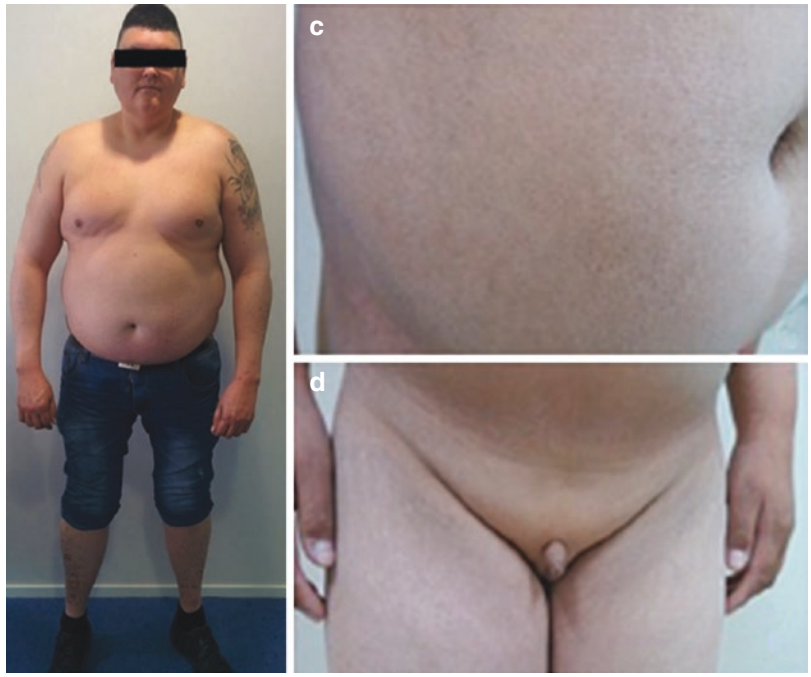
Kallmann Syndrome



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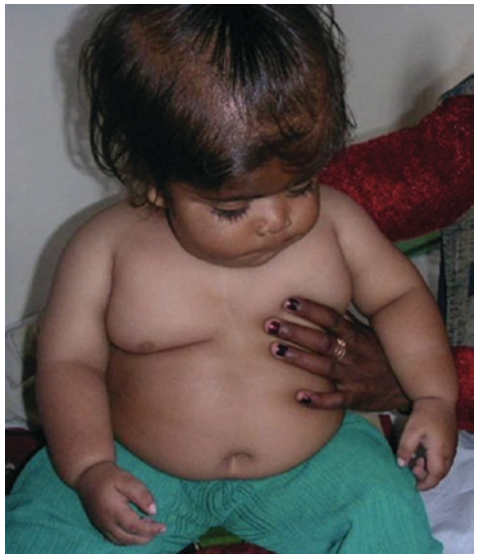
Reproduced with permission by Berges-Raso et al. [95]. https://pubmed.ncbi.nlm.nih.gov/30352392/

Kleefstra Syndrome

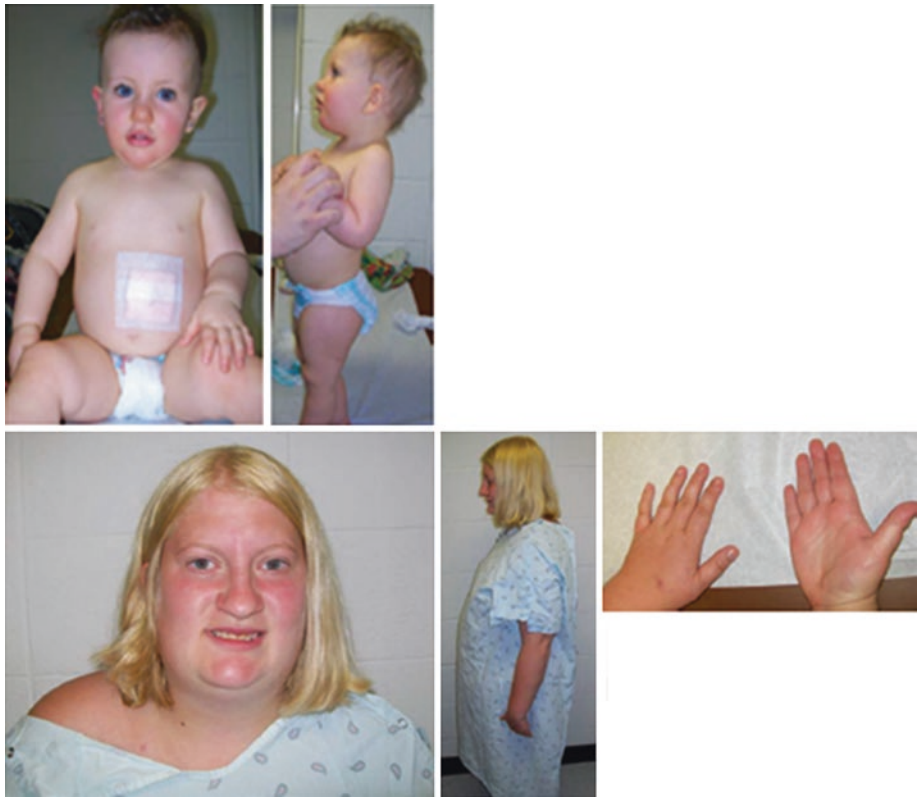
Reproduced with permission by Torga et al. [96]. https://pubmed.ncbi.nlm.nih.gov/30370152/

MOMO Syndrome



Reproduced with permission by Sharda et al. [97] https://pubmed.ncbi.nlm.nih.gov/23074680/

Prader-Willi Syndrome



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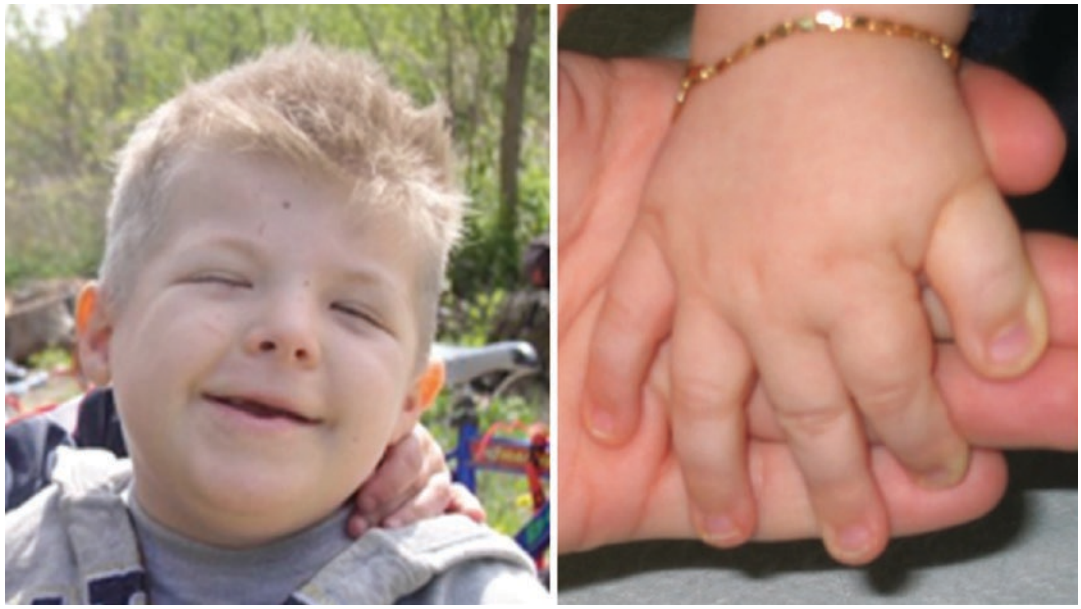
Rubinstein-Taybi Syndrome



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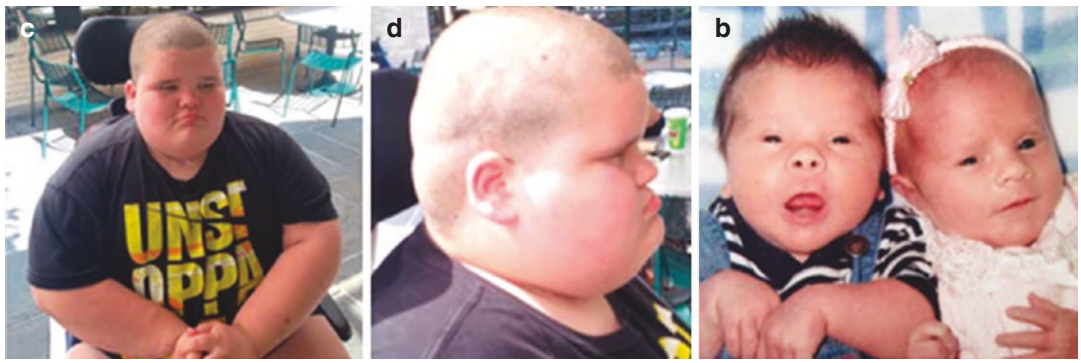
Smith-Magenis Syndrome



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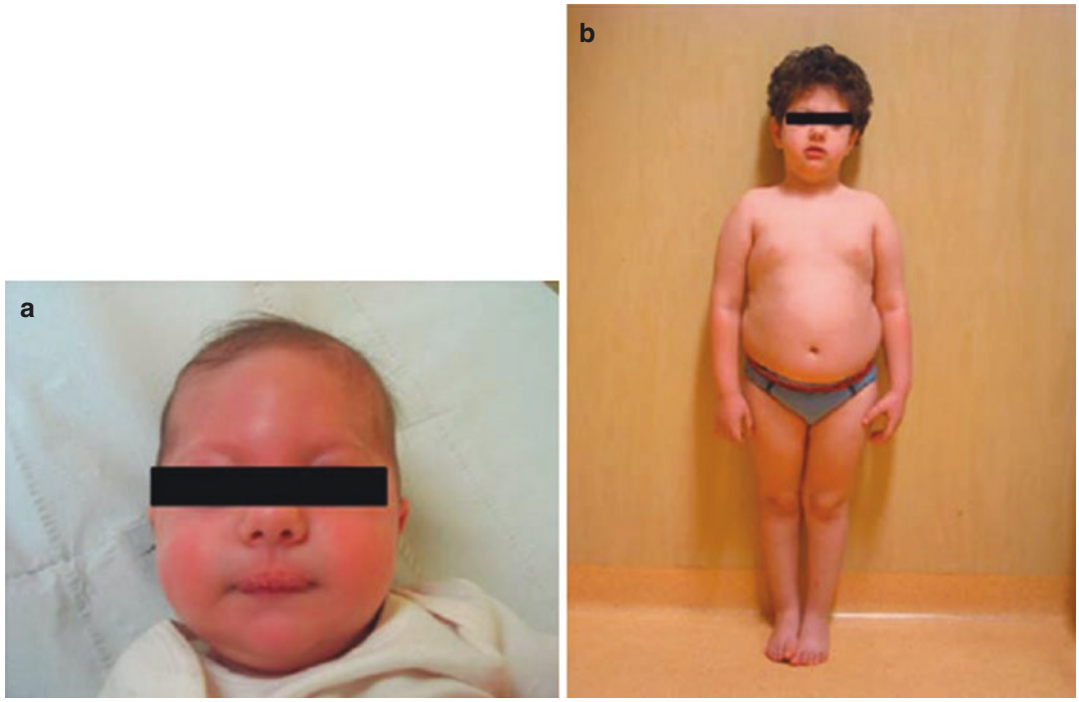
Temple Syndrome



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WAGR Syndrome

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Conclusions

Description of monogenic and syndromic causes of obesity in humans with introduction to genetics and background information is provided. Chromosome ideograms showing the location of recognized obesity genes reported in the medical literature playing a role or contributing to human obesity along with a list of single genes associated with obesity are made available for the readership. Images of individuals with recognized examples of obesity-related genetic syndromes are provided along with clinical descriptions, genes involved, inheritance patterns, and pertinent references per syndrome, which are generated regarding these disorders with a goal to provide an updated review and status of our understanding of monogenic and syndromic obesity.

The field of syndromic obesity and causation related to single gene and/or copy number variants is emerging as an important area for basic and translational research due to the worldwide obesity epidemic, particularly in westernized societies. Heritability estimates as high as 70% are reported supporting the role of at-risk genetic factors requiring a better understanding of their involvement in both exogenous or simple obesity as well as syndromic forms of obesity to improve healthcare management and quality of life for those afflicted. This chapter potentially serves as a framework to gain insight into monogenic (single gene) and syndromic causes of obesity in humans.

Advances in genetic technology are increasing exponentially and offer application to further elucidate potential contributions to disease states including obesity. Understanding the genetic basis of syndromic obesity will elucidate specific biological underpinnings and should lead to new discoveries applicable to care and treatment and lessen the burden of obesity in our society. A growing technological field of molecular genomics promises identification of genetic defects and elucidation of gene-gene and protein interactions with protein modeling. Genotype-phenotype correlations assist in understanding biological pathways, inheritance, and molecular mechanisms including gain or loss of gene function. The description of the biological processes controlling and regulating appetite, energy expenditure, and balance is reviewed and discussed in this report. We anticipate continued stimulation of research focused on targeted therapeutics for monogenic or syndromic causes of obesity. This in turn will encourage clinical trials for treating exogenous and syndromic obesity (e.g., Bardet-Biedl, Prader-Willi). A systematic assessment of the causes and biomarker development can potentially improve both prenatal and postnatal diagnosis leading to early recognition of risk factors for obesity. This knowledge is essential to thwart the complications of obesity and may contribute directly to selection of management and treatment options to lessen health issues, associated comorbidities, and mortality. Health complications of excessive obesity, either due to single gene defects or syndromic obesity, require close surveillance and multidisciplinary clinical treatment approaches.

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Part II

Medical Physiology and Treatment

Medical Considerations

5

Urs Eiholzer and Phillip D. K. Lee

Over the past three decades, a rapidly increasing wealth of information has accumulated regarding the medical pathophysiology and treatment of Prader-Willi syndrome (PWS). Clinical diagnostic criteria and acceptance of genetic diagnostic testing in the 1990s helped to focus clinical and research attention on a condition which had been largely disregarded as a defined clinical entity. The identification of a defect in the growth hormone (GH) system and, moreover, demonstration of GH treatment efficacy provided the first and, to date, only treatment for PWS to attain regulatory approval in 2000. Advances in molecular biology have provided valuable tools for linking genetic findings to phenotype. Although there has been considerable progress since the last edition of this book [1], there is a continuing lack of systematic information regarding many of the morbidities associated with PWS.

This chapter provides an overview of medical concerns in PWS and discussion of conditions that are not addressed in successive chapters. The next chapter addresses topics related to the gastrointestinal system, obesity, and body composition in PWS. The final chapter of this section is dedicated to a review of GH therapy in PWS.

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Natural History and Age-Related Morbidity Without GH Treatment

The natural life history for a typical individual with Prader-Willi syndrome (PWS) (and without GH treatment) can be instructive in providing a logical framework for the succeeding discussions. Various "life stage" classifications for PWS have been proposed, all generally similar in terms of associated morbidities. The life-staging outlined here is primarily for the sake of illustration; PWS-associated morbidities are actually part of a lifelong continuum.

The first stage is in utero. The most notable abnormality at this stage is fetal hypomotility, usually noted by women with previous non-PWS pregnancies. This hypomotility is consistent with hypotonia, a lifelong feature of the syndrome. In male fetuses with PWS, there is an increased risk for testicular maldescent, and genital hypoplasia may occur in both sexes. Scoliosis may also be observed in utero, although this is uncommon in our experience. Hypogonadism and scoliosis, like hypotonia, are lifelong features of the syndrome. No other abnormalities have been noted during fetal life. No abnormalities of the placenta, umbilical cord, or amniotic fluid volume or

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composition have been reported. Increased fetal wastage has not been reported.

The neonate with PWS is usually born at or near term, and no specific abnormalities related to labor and delivery have been noted. A slightly low, but not usually "small for gestational age" birth weight is characteristic. Cryptorchidism, genital hypoplasia, and scoliosis may be noted at birth, along with the characteristic facies. The most striking medical abnormality in the neonatal period is severe whole-body hypotonia, a condition that is virtually universal for infants with PWS. Decreased limb movements, marked truncal hypotonia, weak cry, and decreased neuromotor reflexes are related characteristics. Dysconjugate eye movements (strabismus, but not nystagmus) may be noted. A weak suck reflex and consequent poor feeding occur in all infants with PWS.

For the remainder of the neonatal period, hypotonia and associated morbidities continue to be the number one major medical concern. Failure to thrive is a common diagnosis, often leading to valiant efforts to facilitate nutrition and weight gain. However, it should be noted that obesity, defined as increased body fat relative to lean mass, is present even in these underweight infants with PWS [2]; feeding maneuvers may improve weight gain while doing little to improve mass and function. However, severe undernutrition may have detrimental effects on bone growth and brain development.

Apnea and hypoventilation may be observed in the neonatal period and are nearly universal on formal testing. Neuromotor and speech developmental delay, the latter probably due to a combination of oromotor hypotonia and central cognitive defects, are also usually first evident in infancy.

The toddler stage, defined by independent ambulation, has a markedly late beginning in children with PWS, usually after 2 years of age. Although markedly decreased muscle mass and hypotonia continue during this period, the available muscle fibers progressively strengthen and gain sufficient function to enable food gathering and oromotor function, essentially unmasking intrinsic hyperphagia and greatly increasing the risk for obesity. Problems with apnea and hypoventilation may appear to abate during this period. Scoliosis may progress with ambulation and height growth. Physical therapy can markedly improve physical function during childhood, although hypotonia is still evident.

One of the paradoxes of childhood growth in PWS is that linear growth will often decelerate as weight gain accelerates, typically beginning at about 2 years old. Height percentiles will continue to decline throughout childhood, while body fat increases, with the 50th percentile for PWS approximating the 3rd percentile for the reference population [3]. A major exception with regard to height deceleration are those children with PWS who develop premature adrenarche, a condition that can result in normal or accelerated height velocity but, unlike in non-PWS children with premature adrenarche, results in severely compromised final adult height due to premature epiphyseal closure.

Adolescence is marked by incomplete sexual maturation. Adrenarche is usually normal or premature, but males with PWS rarely progress past mid-puberty, and girls often fail to have menarche. Because of the hypogonadism and deficiencies in the growth hormone system, the usual pubertal growth spurt is blunted without GH treatment. Scoliosis, if present, can become particularly problematic starting in late childhood. Excessive gain of body fat also tends to progress rapidly, accompanied by increased risks for weight and body fat-associated morbidities. Unlike with usual exogenous obesity, bone mineral density may be relatively low in adolescents with PWS, a problem that tends to persist into adulthood.

The natural medical history of adults with PWS is relatively unstudied. Although most young adults with PWS can enjoy a semi-independent life, significant physical disability is evident. The combination of overweight and hypotonia can contribute to wheelchair-dependence in some cases and respiratory insufficiency in most cases. In addition, osteoporosis, often caused or accentuated by untreated hormonal deficiencies, and scoliosis can also lead to significant morbidity.

Mortality

The natural life span and natural age-related mortality of individuals with PWS are incompletely undefined. Experience suggests that survival past the fifth or sixth decade is unusual. For instance, in a survey of 232 adults with PWS, the oldest was 62 years old [4]. Perhaps because of the obvious features of overweight and obesity, an anecdotal assumption has been made that many, if not most, individuals with PWS succumb to cardiovascular complications related to obesity. However, available data suggest that this may not be the case. As reviewed in other sections, insulin resistance does not appear to occur in the majority of adults with PWS. Atherogenic lipid profiles have also not been observed with increased frequency, and atherosclerotic heart disease has not been reported. Personal experience and recent data indicate that the major cause of overall mortality in PWS is respiratory insufficiency or cardiorespiratory failure. In many cases, demise appears to be triggered by acute or chronic pulmonary infection. It appears likely that underlying poor respiratory effort due to hypotonia may be a major contributing factor.

In one of the first detailed case series, Laurance et al. [5] found 24 individuals with PWS alive after age 15 years old (15–41 years of age) and 9 deaths; 4 deaths occurred before 15 years old and 5 between 17 and 23 years old. Cardiorespiratory failure was the proximate cause of death in these cases.

A population-based survey in England included 66 individuals with PWS, birth to 46 years old; 25% were found to have type 2 diabetes mellitus, and 50% had recurrent respiratory infections [6, 7]. Other morbidities included ulcers of the lower extremities (22% of adults), scoliosis (15% in children), and sleep disorders (20%). Limited data from this study indicated an extrapolated lifetime mortality rate of >3% per year; an updated analysis lowered this estimate to 1.25% per year [8].

An international review of mortality in PWS found 13 deaths in individuals under the age of 5 years and 14 deaths in individuals older than 9 years [9]. Of the 13 deaths in younger individuals, 9 were due to respiratory failure, and 2 others were judged to be "sudden" following onset of gastrointestinal symptoms and fever. In the 14 older individuals, pneumonia was contributory in 3 cases and cardiorespiratory failure in 1. Of the other deaths in the older group, two were thought to be due to gastric dilatation, two had uncertain cause, and there were single cases of myocardial infarction, stroke, familial cardiomyopathy, femoral thrombosis, spinal myelitis, and malignancy. Nine of the younger and only three of the older patients were autopsied.

In a study of 36 adults with PWS in Australia, there were 10 deaths at a mean age of 33 years (range 20–49 years); 3 were due to pneumonia or cardiorespiratory arrest, 1 was due to respiratory illness complicated by congestive heart failure, 2 were undetermined, and there were single cases of hypoglycemia, myocardial infarction, stroke, and pulmonary embolus [10].

A population-based study in Flanders of all patients diagnosed by DNA methylation analysis found no individuals with PWS over age 56 years and a marked drop in numbers of cases with age, particularly after age 32 years [11]. Seven cases of death were reviewed: three children succumbed to pneumonia and respiratory failure, and four adults died from various causes—respiratory infection, cardiorespiratory failure, stroke, and car accident.

Respiratory problems were thought to be possibly contributory in five of eight deaths (5 months to 43 years of age) [12]. Small adrenal size was identified in three of four autopsied patients in this latter series but was not reported in another series of seven autopsies [9].

Medical Concerns

Numerous medical conditions have been associated with PWS, with varying degrees of published documentation. For the purposes of discussion, PWS-associated physiology, pathophysiology, and medical morbidities will be grouped as follows:

This Chapter: Medical Considerations

I. Disorders of Sexual Development and Maturation
   A. Genital Hypoplasia and Cryptorchidism
   B. Hypogonadism
II. Musculoskeletal Disorders
   A. Hypotonia
   B. Scoliosis
   C. Osteoporosis
   D. Hip Dysplasia
III. Respiratory and Circulatory Disorders
   A. Respiratory Disorders
   B. Cardiovascular and Cerebrovascular Systems
IV. Miscellaneous Medical Concerns
   A. Thermoregulatory Disorders, Autonomic Dysfunction, and Anesthesia Risk
   B. Ophthalmologic Disorders
   C. Sensory Function and Dermatillomania
   D. Mitochondrial DNA
   E. Epilepsy
   F. Cancer
   G. Infection

Chapter 6: Gastrointestinal System, Obesity, and Body Composition

I. Gastrointestinal System and Disorders
   A. Oropharynx
      1. Salivation
      2. Feeding and Swallowing
   B. Stomach
      1. Mechanical Function
      2. Digestion
   C. Intestines
   D. Pancreas and Liver
II. Obesity and Nutrition
   A. Overweight and Obesity
      1. Diagnosis
      2. Pathogenesis
         (a) Overweight and Body Composition
         (b) Energy Expenditure
      3. Associated morbidities
   B. Treatment
      1. Nutritional Strategies
      2. Special Nutritional Considerations
      3. Associated Morbidities
III. Measurement of Body Composition
   A. Review of Methodologies
   B. Summary Comments

Chapter 7: Growth Hormone

I. Background
II. Growth Hormone Treatment
   A. Efficacy of Treatment in Children with PWS
   B. GH Treatment of Adults with PWS
   C. Adverse Effects
III. Summary and Conclusions

Based on clinical experience and published studies, disorders that do not occur with increased frequency in PWS include the following:

1. Thyroid dysfunction [13–18]
2. Hyper- or hypoprolactinemia [14, 16, 17, 19]
3. Adrenocortical dysfunction [13, 16, 18, 20, 21]
4. Abnormal melatonin secretion [17]
5. Parathyroid hormone disorders
6. Intrinsic defects in calcium or vitamin D metabolism
7. Dyslipidemia [22, 23]
8. Type 1 diabetes mellitus
9. Autoimmune or immunodeficiency disorders
10. Disorder of the renin/aldosterone/angiotensin [13] and antidiuretic hormone systems
11. Renal and hepatic disorders
12. Primary lung diseases, including asthma
13. Disorders of olfaction and taste [24, 25] (not including food preference)
14. Hearing disorders, although auditory and visual processing disorders have been reported [26]
15. Slipped capital femoral epiphysis [27]

Disorders of Sexual Development and Maturation

Genital Hypoplasia and Cryptorchidism

Pathophysiology

Genital hypoplasia is a frequent finding in neonates with PWS, occurring in 13 of 15 cases

(86.5%) reviewed for derivation of infant diagnostic criteria [28, 29].

In male infants with PWS, cryptorchidism is reported in >90% of cases; most cases are bilateral [30, 31]. In comparison, cryptorchidism occurs in 5% or less of non-PWS infant males [32]. It is clinically important to distinguish true cryptorchidism from retractile and gliding testes, although the evaluation and treatment of these conditions is similar. Small testes and scrotal hypoplasia, although usually not bifid scrotum, are also reported in most cases of PWS [31], whereas micropenis is reported in less than 50%. Increased occurrence of hypospadias has not been reported in males with PWS. Prostate and ductal systems have not been fully characterized, although anecdotal reports indicate that the testicular accessory structures are often noted to be hypoplastic at surgery.

Genital abnormalities in female infants with PWS have been more difficult to characterize, although neonatal labial hypoplasia has been reported [31, 33]. Hypoplasia of the clitoris and/or labia minora was noted in 32 of 42 females with PWS (76%) evaluated at a mean age of 17.5 years [31]. The internal female genital anatomy has not been characterized, although no specific abnormalities of Müllerian duct derivatives have been described. In addition, no cases of inappropriate virilization or appearance of male structures have been reported.

Clues to possible mechanisms for the fetal genital malformations in PWS can be gleaned from the nature of the observed abnormalities and knowledge of normal fetal genital maturation, which has been extensively reviewed in the literature [34, 35] and is briefly summarized here.

In the male fetus, the first evidence for sexual differentiation, the appearance of the seminiferous cords and Sertoli cells, occurs at ~6–7 weeks of gestation. Leydig cell production of testosterone is first detectable before 9 weeks of gestation. Müllerian (female) duct regression occurs between 7 and 10 weeks, overlapping with Wolffian (male) duct differentiation between 8 and 12 weeks.

For the male external genitalia, elongation of the genital tubercle is noted by 8 weeks. By 16 weeks of gestation, urethral closure with penile formation and fusion of the labioscrotal folds are complete. All of these events, and the formation of the prostate, are dependent upon the production of testosterone by the fetal Leydig cells and conversion to dihydrotestosterone, via the action of 5α-reductase Type II in the target tissues. The external genitalia experience further growth and less significant differentiation after approximately 13–14 weeks of gestation.

The testes originate at 7–8 weeks of gestation in proximity to the inguinum and kidneys and are apparently anchored in place by the gubernaculum, a gelatinous structure that attaches the lower pole of each testis to the inguinal region. Testicular descent has been divided into two stages [36]. The first stage, occurring at 8–15 weeks of gestation and sometimes termed transabdominal descent, involves cranial migration of the kidneys and other structures, while the testes remain in place. The gubernaculum enlarges in an androgen-independent process that may be facilitated by testicular production of insulin-3 (also known as descendin), creating a path in the inguinal canal for future testicular descent. The inguinal canal is formed by differentiation of musculature surrounding the gubernaculum. During the second stage, at 28–35 weeks, the patent processus vaginalis protrudes through the internal inguinal ring, thereby transmitting intra-abdominal pressure to the gubernaculum [37]. This is thought to cause movement of the gubernaculum through the inguinal canal into the scrotum, thereby guiding initial testicular descent. Descent of the testes is dependent on gubernaculum-dependent development of the inguinal canal and on the sporadic increases in intra-abdominal pressure induced by the effects of fetal respirations and hiccupping in the presence of functionally intact abdominal wall musculature [37, 38]. After descent, the gubernaculum regresses through an androgen-dependent mechanism. Androgens may also influence the development of musculature involved in the formation of the inguinal canal and optimization of intra-abdominal pressure.

Although fetal gonadotropin production is evident by 9–10 weeks, the early stages of testicular differentiation, androgen production, and

genital development are likely maintained by placental chorionic gonadotropin, which is the predominant fetal gonadotropin through gestation. However, during late gestation, production of LH and possibly other fetal pituitary hormones appears to be necessary for completion of external genital development, genital growth, and testicular descent, as evidenced by the common findings of micropenis and cryptorchidism in cases of congenital hypopituitarism (non-PWS).

Each stage of male fetal sexual differentiation and development is controlled by time-limited processes that are determined not only by hormonal exposure but also by specific genes with time-limited activity [36, 39]. Therefore, each step described above must occur within a specific "window of opportunity." In addition, the testicular hormones (insulin-3, testosterone) involved in testicular descent are largely active on a local or paracrine, rather than systemic, level. Therefore, unilateral defects in hormone action may lead to unilateral cryptorchidism.

In consideration of this knowledge of male genital embryology, a tentative theory for the occurrence of male genital abnormalities in PWS can be generated. Steps that are not abnormal in PWS include urethral closure and labioscrotal fusion, implying normal testicular differentiation, normal in utero testosterone production, and normal activity of 5α-reductase through 16 weeks of gestation. In addition, the usual location of undescended testes near the inguinal ring or in the inguinal canal in PWS-associated cryptorchidism implies normal androgen-independent transabdominal descent at 8–15 weeks. The preponderance of bilateral cryptorchidism indicates that unilateral testicular malfunction or structural abnormality is not involved. Finally, the not uncommon occurrence of bilaterally descended testes and the lesser occurrence of micropenis suggest that the genital abnormalities are not intrinsic to the genetic defect per se but may be secondary to other factors that occur with variable severity from one affected individual to another. A possibility is that cryptorchidism in PWS is may be due to fetal hypotonia, leading to inadequate intra-abdominal pressure [40, 41].

In females, the labial folds, clitoris, and vestibule with single perineal opening are evident by 11 weeks of gestation. Between 11 and 20 weeks, the labia majora, derived from the genital swellings (scrotal anlage in the male), continue to enlarge. However, the labia minora, derived from the genital folds (~the penile shaft in the male), and the clitoris, derived from the genital tubercles (~the glans penis in the male), show little change during this period. At 23–25 weeks, the labia minora enlarge and protrude past the labia majora, and the dual openings (urethra and vagina) move to the perineum. Thereafter, the labia majora become more prominent. Fetal pituitary gonadotropin levels peak at 20–24 weeks (FSH >LH) in the female, and a maximal number of ovarian primordial follicles are observed at 22–24 weeks, possibly stimulated by the FSH peak. In females with PWS, the major external genital abnormality has been noted to be hypoplastic labia minora and a small clitoris, structures that show maximal growth immediately following the fetal gonadotropin surge. Therefore, it appears likely that, as with males with PWS, the external genital abnormalities in some female infants with PWS may be related to a deficiency of fetal gonadotropin secretion.

Evaluation

Any male neonate with unexplained hypotonia and cryptorchidism with or without micropenis should be suspected of having PWS, especially if there are no other anogenital abnormalities. Unexplained neonatal hypotonia is, of course, a stand-alone criterion for consideration of PWS testing [42]. Similarly, in females with hypotonia, the presence of hypoplasia of the labia minora and/or small clitoris should further encourage consideration of testing for PWS.

In cases of cryptorchidism, evaluation for the presence of testes and testicular function may be advisable before and after surgical treatment. If the testicle(s) is completely nonpalpable, ultrasound and, in some cases, a magnetic resonance imaging (MRI) may provide additional information. Brain imaging studies are not particularly useful unless there is other evidence for pituitary

or CNS dysfunction; intrinsic structural abnormalities of the central nervous system visible on routine imaging have not been identified in PWS [20, 43].

Single measurements of testosterone, LH, and FSH in the first few days of life or during the expected secondary gonadotropin surge at 30–60 days of age may, if positive, confirm the presence of functional testicular tissue. A testosterone level >20–50 ng/dL (700–1750 pmol/L) is indicative of testosterone production. However, although this random sampling is often useful in non-PWS infants with cryptorchidism, utility may be limited in congenital hypogonadotropic hypogonadism since gonadotropin priming may be necessary for optimal testicular response. Therefore, a negligible random neonatal testosterone level in an infant with PWS does not preclude the existence of functional testicular tissue. Similarly, while normal anti-Mullerian hormone levels may indicate functional testicular tissue, levels may be low in bilateral cryptorchidism [44]. Gonadotropin stimulation testing to document functional testicular tissue is not usually required but may be indicated in those patients with true bilateral cryptorchidism and a low random neonatal testosterone level.

Treatment

Micropenis A stretched penile length of <1.5–2.0 cm could lead to difficulty with toilet training and upright urination, as well as complicate peer relationships [33]; however, scientific data relating to these effects is lacking. A short course of low-dose testosterone may be used to improve the appearance and function of the penis [45, 46].

A typical treatment regimen for micropenis is depot testosterone (enanthate or cypionate), 25 mg by intramuscular injection every 3–4 weeks, typically for three doses. A longer course or higher dose is not recommended since either of these could lead to inappropriate virilization and acceleration of skeletal maturation. Experience suggests that this treatment should be initiated in infancy, preferably before 6 months of age, for maximal effectiveness. There is a theoretical risk for triggering central puberty in older children, although this risk may be minimal in children with PWS. The child should be examined prior to each dose to gauge clinical response and the necessity for additional doses; a stretched penile length ≥2.0 cm is adequate. Particularly in the obese child, the suprapubic fat pad should be fully compressed when obtaining a penile length measurement. On occasion, a few strands of pubic hair and acceleration of linear growth may be observed during the treatment course, but these effects invariably abate within a few weeks after treatment is completed. There is no evidence that such treatment adversely affects later penile growth potential [47].

Cryptorchidism Spontaneous descent of a cryptorchid testicle(s) may occur in a prepubertal or pubertal boy with PWS [48], as it does in a significant proportion of cases of non-PWS cryptorchidism [32], although unlikely after 6 months old [49]. The converse condition, spontaneous ascent of a descended testicle(s) has not been reported in PWS. In other cases, gonadotropin administration, such as the "long" gonadotropin stimulation test described above, may be successful in achieving testicular descent. The success rate of this treatment is low in non-PWS true cryptorchidism [50] but may be better in PWS [51].

In both PWS and non-PWS cases of cryptorchidism, the justification for and timing of surgical exploration and orchiopexy have been controversial. In non-PWS populations, cryptorchidism has been associated with a significantly increased risk for cancer, and this risk may be significantly reduced if surgical correction is performed before puberty and particularly before 18 months old [52–54]. Therefore, it may be somewhat surprising that only three cases of testicular cancer in PWS have been published, seminoma in a 32-year-old [55] and a 40-year-old man [56] and a germ cell neoplasm in a 9-year-old boy with cryptorchidism [57]. A low

occurrence of testicular cancer has been noted in non-PWS individuals with cryptorchidism and hypogonadotropic hypogonadism [58], an observation that may be relevant for PWS. Facilitation of physical surveillance for torsion and testicular tumors has also been proposed as a justification for orchiopexy.

Preservation of testicular function and fertility has been given as another reason for treatment of cryptorchidism. In a study of 1335 non-PWS boys with cryptorchidism, an increased risk for germ cell absence was noted after 15–18 months of age, and this was associated with adult infertility in a follow-up study, while surgical correction prior to this time appeared to preserve fertility potential [54, 59]. Fertility has not been reported in men with PWS; the lack of germ cells has been found on testicular biopsy [13, 60, 61], although as noted above germ cell tumors have been reported and normal testicular histology has been reported in some cases [62]. Whether fertility can be induced in men with PWS and whether this is impacted by cryptorchidism are open questions.

Among factors favoring correction of an undescended testis include a risk for traumatic injury for testis located at the inguinal ring. In non-PWS cases, cryptorchidism is associated with increased risk for hernia and hydrocele due to the patent processus vaginalis, although increased occurrence of these conditions has not been reported in PWS. Cosmetic and psychosocial considerations may also be important in some cases.

All cases of cryptorchidism should be evaluated by an experienced pediatric urologist before 6 months of age, with a goal for surgical correction before 18 months old, as in non-PWS individuals with cryptorchidism [52]. However, since infants with PWS may present unique surgical and anesthesia risks, surgical procedures may be delayed and medical therapy initially attempted. Orchiopexy may be particularly difficult in PWS due to the degree of maldescent and hypoplastic accessory structures. Either before or after surgery, the testicles may be atretic and nonfunctional, and experience suggests that the risk for post-orchiopexy testicular retraction and degeneration is high. In some cases, removal of the testicular tissue with or without placement of prostheses may be a preferred or necessary option.

Hypogonadism

Pathophysiology

Puberty normally occurs as a two-system process, beginning after 8 years of age: adrenarche, with physical signs sometimes referred to as pubarche, and gonadal maturation or gonadarche.

Adrenarche involves production of adrenal androgens, resulting in secondary sexual hair growth (pubic and axillary hair); this effect is superseded in males by testicular production of testosterone. The control of adrenarche at puberty is not completely defined. In boys, gonadarche involves testicular production of testosterone, resulting in masculinization. In girls, gonadarche includes ovarian maturation and estrogenization. Gonadarche is controlled by the pituitary production of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), which are in turn controlled by hypothalamic production of gonadotropin-releasing hormone (GnRH).

The hormonal milieu associated with adrenarche (elevated adrenal androgen precursors) is initially present in the fetus and persists into the first few months of postnatal life. Pubertal levels of gonadotropin and associated gonadal steroid levels also occur during fetal life, are suppressed at birth, then recur as a minipuberty at 1–3 months of age, and then taper to prepubertal levels, typically by 6–9 months. The mechanisms for this suppression and subsequent reactivation during puberty are incompletely understood.

In PWS, adrenarche usually occurs normally in both sexes, although a relative decrease in secondary sexual hair has been anecdotally reported. A significant proportion of children with PWS have premature adrenarche, perhaps related to insulin resistance or decreased insulin sensitivity, although insulin levels are typically low in PWS [63–66].

On the other hand, gonadarche is usually abnormal in PWS, with incomplete pubertal (sexual) development occurring in more than 80% of adolescents and adults with PWS [29, 31]. Many female patients with PWS progress through phenotypic puberty (e.g., breast development) and experience menarche (an initial menstrual period) but may subsequently fail to have normal menstrual cycles and/or have early

menopause. Breast development can progress to full maturation, although 49 of 81 individuals (64%) in a survey study were reported to have small or flat breasts [4]. Most males with PWS fail to progress past mid-puberty. Complete primary gonadal failure is infrequent except in cases of acquired testicular atrophy [67], and there is a single report of abnormal ovarian histology in PWS [13]. In addition, treatment with gonadotropin or gonadotropin-releasing hormone can result in improvement or normalization of gonadal function [13, 68], implying that gonadal steroidogenesis is not a primary disorder.

As discussed above, hypogonadotropic hypogonadism probably does not occur in utero. Minipuberty, with elevated gonadotropin and testosterone levels, has been reported in infant males with PWS, limited data are less convincing in females [40, 41, 69]. The occurrence of minipuberty argues against infantile hypogonadotropic hypogonadism. Although gonadotropin response to exogenous GnRH may be absent or low in preteen children with PWS [70], this may be considered a typical prepubertal pattern in non-PWS children and not necessarily indicative of pathology.

In adolescents and adults with PWS, low baseline and GnRH-stimulated gonadotropin levels are a frequently reported finding which has been used to support an argument for an intrinsic hypogonadotropic hypogonadism, i.e., at the hypothalamic or pituitary level. On the other hand, multiple observations indicate that irreversible, complete intrinsic gonadotropin deficiency at the pituitary or hypothalamic level may not be involved [71]. Spontaneous menses are often observed [13, 33, 72], and several cases of male central precocious puberty have been reported [62, 73]. Elevated gonadotropin secretion has been observed with primary gonadal failure, arguing against intrinsic gonadotropin deficiency [67, 74, 75], although the degree of elevation may be less than expected in non-PWS cases.

Clomiphene citrate, a triphenylethylene estrogen antagonist, has been observed to stimulate gonadotropin secretion and gonadal function (including menses and spermatogenesis) in males and females with PWS [13, 48, 76, 77]. In non-PWS individuals, clomiphene has been used for induction of gonadotropin secretion and ovulation during treatment of female infertility [78]. As an estrogen analog, clomiphene binds to intracellular estrogen receptors in the arcuate nucleus of the hypothalamus, thereby blocking estrogen inhibition of gonadotropin-releasing hormone (GnRH) secretion, resulting in stimulation of pituitary gonadotropin secretion. Clomiphene also appears to sensitize the pituitary gland to GnRH action, but direct effects of clomiphene to stimulate pituitary gonadotropin secretion have not been found. Therefore, clomiphene stimulation of gonadotropin secretion and action in individuals with PWS argue against an intrinsic or complete hypothalamic or pituitary GnRH or gonadotropin defect.

Induction of menses in PWS has also reported with the use of fluoxetine [79], a selective serotonin reuptake inhibitor (SSRI) not uncommonly used for psychopharmacologic treatment of PWS. Induction of menses has been reported in a 25-year-old woman with PWS during treatment with another SSRI, citalopram [80]; this patient subsequently became pregnant after withdrawal of citalopram, although her menses had become "sparse." SSRIs are thought to act by inhibiting neuronal reuptake and metabolism of serotonin (5-hydroxytryptamine, 5-HT), thereby increasing the local concentration and activity of serotonin. Serotonin-secreting neurons originate primarily in the midbrain and extend throughout the central nervous system. The role of serotonin in gonadotropin secretion has not been completely defined; however, it appears to affect pulsatile hypothalamic GnRH secretion [81]. Therefore, these cases provide additional arguments against an intrinsic complete GnRH/gonadotropin deficiency in PWS.

A possible mechanism for partial, variable deficiency in gonadotropin secretion in PWS is suggested by rodent studies in which disruption of *Ndn*, an imprinted gene located within the PWS region that codes for necdin (neurally differentiated embryonal carcinoma cell-derived factor), results in a 25% reduction in GnRH neurons in the hypothalamus [82] and may be involved in the development of GnRH neurons [83]. However, corollary studies in humans have not been reported.

As mentioned previously, male fertility has not been reported in PWS, and testicular biopsy has usually but not always shown Sertoli cell-only histology, i.e., the presence of Sertoli cells, which provide the milieu for spermatogenesis, and Leydig cells, which produce testosterone, but the absence of germinal cells (spermatogonia) [13, 60–62]. It is uncertain whether this is due to the lack of LH stimulation of Leydig cell testosterone production (a requirement for spermatogenesis) or the lack of FSH stimulation of Sertoli cell mitosis and/or some other factors. The reported induction of biopsy-confirmed spermatogenesis with clomiphene in a young adult with PWS [48] suggests that the abnormal histology is not due to an intrinsic testicular defect.

Fertility in PWS may also be limited by social factors. Most adults with PWS are not married and, presumably, have limited sexual contact. Social limitations to fertility may be altered as advances in medical and behavioral treatment improve physical outcomes and lifestyle choices.

Evaluation

Adolescents with PWS and clinical evidence of hypogonadism, as described above, will usually have low gonadotropin secretion unless a primary gonadal defect is present. For research purposes or in equivocal cases, serum FSH and LH levels can be measured at timed intervals following intravenous administration of GnRH [70, 84]. Clomiphene pretreatment may augment gonadotropin secretion.

In cases where testicular atrophy or necrosis is suspected, elevations of gonadotropin and low levels of testosterone can be expected if there is significant primary gonadal failure. Primary ovarian failure has not been reported in PWS; however, elevated (e.g., menopausal) gonadotropin levels may be expected in such a case. Despite the obesity, there does not appear to be an increased occurrence of polycystic ovary syndrome in PWS.

Fertility testing is rarely clinically indicated in PWS.

Treatment

Virtually all males with PWS fail to progress past mid-puberty, and testosterone levels are usually low relative to the adult normal range. Androgen replacement therapy has been somewhat controversial, primarily due to anecdotal concerns that testosterone treatment might cause inappropriately aggressive behavior or worsen other behavioral problems, although there are no published data showing such a relationship. On the other hand, testosterone therapy, combined with psychotherapy, was reported to improve behavior in an adolescent with PWS [46]. In addition, detailed studies in non-PWS eugonadal and hypogonadal men have not shown an effect of physiologic or moderately supraphysiologic levels on measures of aggression [85]. Our experience suggests that testosterone replacement should be started at a biologically appropriate time, i.e., in early adolescence; late initiation of therapy may be associated with adverse psychosocial outcome, perhaps due to an impact on the socialization process [71].

Although there is considerable current controversy regarding efficacy and safety of testosterone treatment of older men with low testosterone levels, there is little doubt that childhood-onset male hypogonadism should be treated as a lifetime condition [86]. Normal adult testosterone levels are considered to be necessary for completion of sexual development, preservation of bone and muscle mass and function, and prevention of osteoporosis in males with childhood-onset hypogonadism. Since osteoporosis and hypotonia are major causes of morbidity in PWS and hypogonadism is common, testosterone replacement therapy would appear to be medically advisable.

In recent years, new delivery systems for testosterone replacement have become available. A traditional treatment is intramuscular injection of 200 mg depot testosterone once or twice monthly, which causes an acute supraphysiologic rise over 24 hours, followed by a steep decline to subnormal levels over 2–3 weeks. If supraphysiologic levels of testosterone have even minor effects on mood and behavior, then the depot injection may cause inappropriate swings in these parameters. Longer-acting testosterone preparations, such as long-acting testosterone undecanoate injection, may avoid these swings in testosterone levels and potential behavior effects.

Testosterone patches are available at several dose levels. The patches are changed daily, can be applied to any skin area (the back, thighs, and buttocks are particularly convenient), and the 5 mg patch usually achieves low-normal adult testosterone levels. Anecdotal experience indicates that pruritis and skin picking at the patch site have not been a problem, even in patients who have skin picking in other areas. Testosterone gel preparations are also available, although precautions must be taken to avoid cross-contamination of females and prepubertal males.

Estrogen replacement therapy, usually combined with progestin, is an established therapy for non-PWS hypogonadal women. This treatment has been shown to have multiple benefits, including preservation of bone mass and reduction of fracture risk. However, estrogen replacement in women with PWS is not as well established. Most women with PWS have evidence of estrogen effect (breast development), and menses may occur, although usually irregular. Osteoporosis is a known morbidity in adult women with PWS; however, there are no published data showing efficacy of estrogen replacement. Nevertheless, estrogen replacement may be advisable in women with PWS, particularly in the presence of amenorrhea or oligomenorrhea and/or osteoporosis.

Hypogonadism in women can be treated with oral or transdermal forms of estrogen in combination with progestins or micronized progesterone. Commercial birth control preparations are often used for convenience, are anecdotally well tolerated, and are probably the most commonly prescribed modality in our experience. However, in view of the low reported resting energy expenditure and predisposition for adiposity of Prader-Willi syndrome patients and the report of divergent effects of oral vs. transdermal estrogen on lipid oxidation and fat accumulation [87], it could be argued that non-oral forms of estrogen might be physiologically preferable in this population. In addition, in consideration of the increasing use of growth hormone therapy in adults with PWS, the growth hormone replacement dose required for comparable response in growth hormone-deficient non-PWS women taking oral estrogen was more than double that of women on transdermal estrogen [88]. Thus, treatment with transdermal estrogen with oral progestin (to reduce endometrial cancer risk) or a combined estrogen-progestin patch may be preferred, although there is limited experience and no published data using these preparations in PWS.

Testosterone or estrogen replacement therapy should be coupled with careful monitoring of clinical and behavioral status and bone mineral density. Testosterone levels may be useful in adjusting the patch or gel dose. Monitoring of other biochemical parameters (coagulation profiles, liver enzymes, prostate-specific antigen) may be advisable in some cases. Prostate or gynecologic examinations should also be considered, as appropriate.

In either males or females with PWS who are unable to tolerate gonadal steroid replacement, bisphosphonate therapy can be considered for treatment or prevention of osteoporosis, as has been recommended for similar situations in non-PWS women. Bisphosphonate treatment may also be used as an adjunct to gonadal steroid replacement in cases with severe osteoporosis.

Sexual activity and risks for sexually transmitted diseases are a reality and concern in the treatment of PWS. Therefore, all adolescents and adults with PWS should receive appropriate education and counseling, with testing for sexually transmitted disease when clinically indicated. Contraception and pregnancy testing may be a consideration, particularly for women with menses. Serial measurements of inhibin B may provide a marker of fertility in cases when this is a concern.

Musculoskeletal Disorders

Hypotonia

Hypotonia is a universal feature of PWS, manifesting in fetal life as hypomotility and continuing as a lifelong condition. Neonatal hypotonia is considered to be the key criterion for clinical suspicion of PWS in neonates [29, 42, 89]. The proximate etiology of the hypotonia is decreased

muscle mass, but the pathogenesis of this condition is unknown. Neuromuscular studies, including electromyography and nerve conduction velocity studies, are usually normal [29]. Muscle ultrasound has not identified any abnormalities [90]. A few autopsied cases showed cerebellar changes that could cause motor dysfunction [91, 92]; however, these findings do not explain the decreased muscle mass and related neuromuscular features.

Histologic and ultrastructural studies of muscle fibers in PWS are limited. No morphologic changes are identified on routine staining and microscopy, and the fibers appear mature [93, 94]. In one infant, there was a relative paucity of Type 1 fibers and a preponderance of small Type 2 fibers [95]. In a study of 11 PWS infant muscle biopsies, the Type 1 fibers showed increased size variability, and nonspecific abnormalities of Type 2 fibers were noted [94]. However, examination of muscle fibers generally shows minimal, if any, abnormality [93, 94, 96]. Ultrastructural analysis in one case showed increased subsarcomeric accumulation of normal-appearing mitochondria and sarcomeric Z-line changes. The composite data from these limited studies appear to be more consistent with a peripheral muscular disorder or disuse than to a central nervous system myopathy. A possible contribution of a deficiency in insulin-like growth factor-I (IGF-I), a growth hormone-related growth factor, is suggested by the correlation of IGF-I levels with fat-free mass [97, 98].

Physical therapy is an essential element of treatment for Prader-Willi syndrome. However, data relating physical therapy and improvement in neuromuscular function in PWS are limited. Due to the lack of muscle mass, both strength and endurance are deficient, and the range of innate activity can be quite variable [99]. The usual functional improvement in muscle function during infancy and childhood may be due to strengthening of existing muscle fibers rather than to significantly increased muscle mass per se. A 6-month aerobic exercise program (walking) led to significant improvement in aerobic capacity, coupled with decreased body fat and weight, in six adults with PWS as compared with a control group ($n = 5$) [100]. A study using brief, daily calf muscle training (repetitive heel lowering on a household stair) in 17 children with PWS (aged 4.4–18.8 years) found a significant decrease in calf skinfold thickness and significant increases in calf circumference, physical activity, and endurance (physical capacity) [101]. The data provide objective evidence that physical therapy can improve muscle mass and function in PWS and that a reduction in muscle mass can be a direct consequence of reduced physical activity.

Growth hormone treatment has also been shown to improve muscle strength and endurance in PWS; this topic is discussed in more detail in Chap. 7. Adrenarche and testosterone replacement therapy have been anecdotally associated with improved muscle function in some patients; however, objective data in PWS are not available.

Scoliosis

Scoliosis, a commonly observed disorder in PWS, can be defined as a lateral spinal curvature (Cobb's angle) of >10 degrees on standing radiograph. Scoliosis may be observed in utero and in the newborn period, suggesting early initiation of pathogenetic mechanisms. However, experience indicates that most cases are diagnosed clinically in childhood, as with non-PWS scoliosis. Notable progression occurs during late childhood and adolescence and continues into adult life when it may be exacerbated by osteoporosis. Laurance et al. [5] found scoliosis in 15 of 24 adults with PWS, 2 of whom received surgical treatment, and a contemporaneous report estimated that >80% of individuals with PWS are affected [102]. In a survey study of 232 adults with PWS, nearly half reported scoliosis that was significant enough to require treatment [4]. A survey of PWS individuals in Italy showed 42 of 72 (59%) with scoliosis, including 12 of 16 deletion cases (75%) [103]. A population survey in the UK found a 15% prevalence of "severe" scoliosis across all age groups [6], and a study in France found an age-related prevalence of scoliosis, with 44 of 66 (66.7%) affected after 10 years old [104].

The pathogenesis of scoliosis in PWS is not completely defined but most likely falls into the category of neuromuscular scoliosis. Congenital or acquired primary vertebral body abnormalities are not commonly observed, and other causes, such as trauma or degenerative disease, are not reported. Although many cases of congenital scoliosis in PWS have been reported, there has been no association with cardiac, spinal cord, renal, or other malformations as occurs with non-PWS idiopathic congenital scoliosis. Scoliosis is often noted in PWS individuals who are not overweight, indicating that weight is not a causative factor.

Neuromuscular scoliosis has been divided into neuropathic and myopathic subcategories [105]. Neuropathic scoliosis is associated with disorders of the upper or lower motor neurons (e.g., cerebral palsy and poliomyelitis, respectively). Myopathic scoliosis is associated with primary muscle disorders, such as congenital hypotonia and muscular dystrophy. Abnormal kyphosis or lordosis (posterior or anterior spinal angulation, respectively, as viewed from the side) is also frequently noted in neuromuscular scoliosis, as it is in PWS [104]. Unlike the more common idiopathic adolescent scoliosis, neuromuscular scoliosis tends to progress through adult life, as observed with PWS scoliosis. Therefore, the described and anecdotal characteristics of scoliosis in PWS most closely resemble myopathic neuromuscular scoliosis, i.e., due to hypotonia of the paravertebral muscles.

The risk for scoliotic curve progression increases with linear (height) growth in idiopathic adolescent scoliosis; longitudinal study data on curve progression in PWS or other forms of neuromuscular scoliosis are lacking, although a cross-sectional study suggests a similar association [104]. Back curvature should be carefully monitored during treatment with growth-promoting therapies, such as growth hormone and anabolic steroids.

The impact of scoliosis on health is not well defined in PWS. Back pain and lower extremity pain are frequent complaints in scoliotic individuals without PWS. However, experience indicates that these complaints are rarely encountered in those with PWS, even in cases with severely abnormal curvatures, possibly related to the PWS-associated deficit in pain sensation.

In infants without PWS, severe curves have been associated with respiratory compromise, but these degrees of curvature are not often observed in infants with PWS. Mild to moderate curvatures (>30 degrees) in adolescents and adults without PWS are thought to cause inefficient coordination of respiratory muscle function and the thoracic cage, resulting in decreased maximal inspiratory and expiratory pressures and reduction in exercise capacity. Compensatory mechanisms involve recruitment of thoracic and abdominal musculature, and this is likely to be deficient in the presence of hypotonia and decreased muscle mass, as is observed in PWS. In non-PWS scoliosis, respiratory symptomatology progressively increases with curves of >70 degrees, with significant risks for respiratory failure at >100 degrees. Experience suggests that a contribution to respiratory compromise is observed with lesser degrees of curvature in PWS; however, published data are lacking.

Excessive kyphosis or lordosis can also be a concern. The normal back has a balanced thoracic kyphosis and lumbar lordosis. Extreme accentuation (hyperkyphosis) or extension of the kyphotic curve into the lumbar region can lead to spinal cord stretching, injury, and paraplegia in non-PWS individuals. Extreme lordosis can be associated with respiratory compromise. Clinical experience indicates that these types of curvature abnormalities are not uncommon in individuals with PWS [104].

Given the high rate of occurrence and the potential associated morbidities, all individuals with PWS should be regularly screened for abnormal back curvature. Some PWS experts have recommended spine radiographs at regular intervals for all patients with PWS, while others recommend regular clinical screening, with radiographs obtained only if indicated by abnormal findings. The Adam's forward bending test is the standard clinical screening procedure for scoliosis, performed with the patient standing with his/her back to the observer and feet together, bending forward with knees flexed and arms extended (hanging).

Abnormal spinal curvature, asymmetric elevation of one shoulder, and/or pelvic tilt should all be indications for further investigation. A similar examination with the patient standing upright, combined with examination of the gait, can also be a useful screening tool. A lateral examination should be performed to detect abnormal kyphotic and lordotic curves. Clinical detection of scoliosis in individuals with PWS may be hindered by obesity, hypotonia, and lack of cooperation; in such cases, radiographic screening may be indicated. Diagnosis is based on the standing radiograph, with anteroposterior (for scoliosis) and lateral (for kyphosis/lordosis) views.

Consultation with an experienced orthopedist is essential as soon as an abnormal curvature is identified, and the treatment plan should be carefully coordinated with other therapies. Treatment of scoliosis in PWS requires conscientious medical observation to determine appropriate timing of treatment. While intermittent spine radiographs may or may not be indicated for routine screening, they are a mainstay of monitoring for progression.

In non-PWS neuromuscular scoliosis, bracing, physical therapy, and weight management are typically used as elements of conservative, nonsurgical management, possibly alleviating symptoms and limiting curve progression; similar results have been observed in children with PWS and milder scoliotic curves [106]. Serial spinal casting for PWS-associated infantile scoliosis may lead to significant curve improvement [107]. Surgical treatment of scoliosis can be difficult in PWS and is generally reserved for progressive, severe (>70 degree) curves. Problems with rod fixation may be due to poor bone and tissue quality [108, 109]. In addition, there can be significant surgical morbidity due to respiratory compromise and infection [110, 111]. Finally, there are limited data regarding efficacy of scoliosis therapy in PWS. In non-PWS individuals with scoliosis, surgical therapy can prevent respiratory compromise; however, similar therapy can be detrimental in cases where lung function is already impaired [112].

Although scoliotic curves may be expected to progress with height growth, particularly during adolescence, there is no evidence that growth hormone treatment increases this risk in children with PWS [113]. The effects of growth hormone on body composition could provide benefit for nonsurgical management of scoliosis and reduce surgical risk.

Osteoporosis

Osteoporosis has been defined as a "skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture" [114]. Bone strength is dependent on both bone mineral and bone quality. However, since overall bone quality and strength are difficult to measure, bone mineral, which accounts for about two thirds of the total bone strength, is commonly used to define osteoporosis.

A complete discussion of normal bone physiology is beyond the scope of this text. However, a few basic principles are essential to understanding bone pathology in PWS. Throughout life, there is continuous loss and gain of bone mineral. During childhood, there is progressive net accretion of bone matrix and subsequent mineralization. Bone mineral density, the amount of bone mineral per unit of bone mass, is relatively low in early life and gradually increases throughout childhood and adolescent growth. Peak bone mass is reached at completion of skeletal (height) growth, and peak bone mineral density occurs in the third decade of life. Thereafter, there is progressive net loss of bone mineral.

Optimal net accretion of bone mass and mineralization during childhood and adolescence is dependent upon several factors, including hormones (growth hormone, gonadal steroids, vitamin D), nutrition (particularly calcium), and neuromuscular stimulation (exercise). Deficiencies in any of these areas could lead to inadequate bone mass accretion and osteoporosis, either in childhood/adolescence or later in life, as the normal loss of bone mineral occurs. Deficiencies of these factors after attainment of peak bone mass will lead to accelerated loss of bone mineral and osteoporosis. In addition, several factors may inhibit or reverse bone mineral-

ization, including chronic use of glucocorticoids, chronic systemic illness, and immobility.

As discussed in other sections, individuals with PWS have low growth hormone, low gonadal steroid levels, and low neuromuscular activity. In addition, vitamin D levels may be low due to the lack of sun exposure, and there may be deficient intakes of both calcium and vitamin D for individuals on calorie-restricted diets. Therefore, it is not particularly surprising that low bone mineral density has been frequently reported in PWS [115–118]. Biochemical markers of bone turnover may also be elevated [118], as might be expected from the probable etiologies. On the other hand, there may be a protective effect(s) of weight, weight-bearing exercise, and/or body fat on bone mineralization [119], although these have not been demonstrated in PWS. Anecdotal experience suggests that decreased bone mineral density in PWS is associated with increased fracture risk and, perhaps, abnormal progression of spinal curvature; there are no published data supporting these associations.

For many reasons, dual-energy X-ray absorptiometry (DXA) has become the standard diagnostic method for assessment of bone mineral density. Most research related to osteoporosis has focused on women, since osteoporosis and fracture risk in postmenopausal women are major public and individual health concerns. Osteoporosis-related fragility fractures in this population are primarily located in the hip and lumbar spine. (A fragility fracture can be defined as a fracture that occurs during normal activity or minor trauma that would not normally cause a fracture in a healthy young adult.) Because of this, standards for diagnosis of osteoporosis are based on DXA analysis of bone mineral density in the femoral neck and the upper lumbar vertebrae (L1–4).

DXA facilities are readily available in most medical institutions. A DXA scan is noninvasive, painless, involves minimal radiation exposure (less than a chest X-ray), and takes only a few minutes. When ordered for assessment of bone mineral status (e.g., to diagnose or monitor osteoporosis), the report typically includes the measured bone mineral parameters and a T-score for the bone mineral density at the hip and spine. The T-score is the standard deviations from the average measurement for a healthy, young, White female at peak bone mass (the reference standard). Therefore, a lumbar T-score of -2.0 means that the L1–4 bone mineral density is 2 standard deviations below the mean for a healthy young, White female. For adult women, fracture risk and definition of osteoporosis is based on the T-score for bone mineral density (or bone mineral content), as follows [114]:

- Normal: T-score between −1 and + 1
- Osteopenia: T-score less than −1 but greater than −2.5
- Osteoporosis: T-score less than −2.5
- Severe osteoporosis: T-score less than −2.5 *and* one or more fragility fractures

It should be noted that osteopenia is not considered to be a disorder, and it is not currently defined as a risk factor for fragility fractures.

All children and adolescents can be expected to have a low T-score since peak bone mineralization has not been attained. Therefore, DXA measurements for children often refer to standard deviation (Z) scores, based on norms established by age, sex, and ethnicity [120], using the same guidelines referred to for T-scores (osteoporosis defined as Z-score less than −2.5). Correction for height and bone age may also be an important consideration, although such corrections are not typically included in the instrumentation software. Adult male standards are also not well defined, and results are usually interpreted relative to the female T-score standard. However, fracture risk has not been defined for T- or Z-score levels in children or adult men.

A caveat with DXA procedures is that results vary considerably according to instrumentation. Technologies vary among manufacturers, and direct comparisons of results are not feasible. Alternate sites (e.g., finger, ankle, and heel) and alternate technologies, such as ultrasound bone density measurements, are also not directly comparable to traditional DXA results and may not be appropriately standardized in relation to age, sex, and fracture risk. Therefore, physicians should be careful to obtain sequential measurements

using a single type of device (e.g., the same body regions measured using a device from the same manufacturer) if the intent is to compare results between procedures.

Although a relationship between bone mineral status and fracture risk has not been established for PWS, many specialists include DXA analyses in the routine care plan for individuals with PWS. Because prevention of osteoporosis and fracture risk is more effective than secondary treatment, DXA screening should begin in childhood or early adolescence, during the period of bone accretion. Even in the presence of a normal DXA analysis, a repeat scan may be advisable if risk factors are present (e.g., hypogonadism, growth hormone deficiency, low activity) to assess the direction and rate of bone mineral changes.

Preventive treatment of low bone mineral density in PWS should include nutritional therapy (vitamin D and calcium supplementation, if needed), hormonal replacement (discussed in other sections of this chapter and in Chap. 7), and exercise. Caretakers should also be aware that individuals with PWS may have decreased deep pain sensation; therefore, bone fractures may not be accompanied by complaints of pain. Unusual gait, posture, or limb movements may signal a need for further investigation.

If there is inadequate accretion of bone mineral, excessive loss of bone mineral, or continuing osteoporosis with or without fragility fractures, bisphosphonate treatment may be advised, particularly for adolescents and adults. Typical regimens involve weekly oral doses of alendronate or risedronate or monthly ibandronate. These oral medications must be administered on an empty stomach with water, with a sufficient subsequent interval before food intake to prevent reflux and esophageal complications. If this type of administration is not feasible, intermittent intravenous bisphosphonate preparations, such as pamidronate or ibandronate, or subcutaneous injections of the non-bisphosphonate, denosumab, can be used. Since osteoporosis-associated morbidity and treatment of osteoporosis has not been well studied in PWS, careful monitoring of individual therapy is necessary. A trial off treatment, with continued annual monitoring of bone density, may be attempted after an adequate bone mineral density has been achieved.

Hip Dysplasia

Hip dysplasia is a congenital condition in which the hip joint socket does not fully cover or support the femoral head. Screening for hip dysplasia is a standard procedure during examination of newborn infants; however, cases can be missed. Untreated hip dysplasia can lead to hip and leg pain, limited mobility, abnormal gait, tears in the hip joint cartilage (labrum), hip dislocation, and degenerative hip disease. A survey study demonstrated a tenfold increase in the prevalence of hip dysplasia in PWS relative to the general population (10% of 565 respondents) [27]; the high prevalence of this condition in PWS was supported in subsequent clinical reports [121–123]. Hip dysplasia was found in a review of 27 of 90 individuals with PWS with relevant imaging studies, ranging from 3 months to 31 years old [124]; many of the cases had not been previously diagnosed. The pathogenesis and reasons for the high prevalence of this condition in PWS have not been defined. However, given the high prevalence, routine monitoring for this condition has been recommended for all children with PWS, including hip ultrasound at 6 weeks old and radiographic studies at 1, 2, 5, 10, and 15 years old [124]. Careful monitoring with delayed treatment has been for hip dysplasia in children with PWS [125].

Respiratory and Vascular Systems

Respiratory Disorders

Physiology

As reviewed above, respiratory disorders, including apnea, sleep-related disorders, and hypoventilation, are a major cause of morbidity in PWS, affecting at least 50% of individuals. In addition, respiratory failure is the major identified cause of mortality.

The control of normal respiration involves complex, interrelated mechanisms under both involuntary and voluntary control. The entire process of respiration involves three primary components: (1) thoracic movement and ventilation or exchange of air between the lungs and atmosphere; (2) exchange of gases (oxygen, CO_2, etc.) across the alveolar membranes; and (3) transport in the circulation, delivery, and exchange in the tissues [126]. The end result is maintenance of tissue oxygen and CO_2 homeostasis. Respiratory disorders in PWS exclusively involve the first component of respiration. No primary abnormalities of the lung tissue or oxygen/CO_2 transport have been identified in PWS.

The first component of respiration is dependent on coordinated neural control of the respiratory musculature, including the upper airway, thoracic muscles, diaphragm, and abdominal muscles. During inspiration, the diaphragm moves down into the abdomen, creating negative pressure in the lungs and influx of air. Additional chest wall muscles may be recruited, especially during exertion. Air entry through nasal and oral paths require coordinated actions of upper airway musculature, including pharyngeal elevation, laryngeal opening, and protective closure (e.g., during swallowing and vocalization). Expiration is primarily a passive event due to elastic recoil of the chest wall and lungs; however, chest wall and abdominal muscles may be recruited during exertion. Due to the high content of Type 1 (slow twitch) and Type 2A muscle fibers, the normal diaphragm is relatively resistant to fatigue. However, the upper airway musculature has a high proportion of fast-twitch fibers and, therefore, a greater susceptibility to fatigue.

The control of breathing is via chemoreceptors that send signals to the central nervous system. Peripheral chemoreceptors in the carotid bodies sense the partial pressure of oxygen (not oxygen content per se), as well as increased PCO_2, acidemia, and low perfusion; these chemoreceptors are not essential for maintenance of respiration. Central chemoreceptors are distributed along the brain stem in several groups; these chemoreceptors respond primarily to increased PCO_2 and decreased pH in the cerebrospinal fluid, both changes resulting in increased respiration.

The automatic rhythmic nature of breathing is controlled by three respiratory centers, located in the brain stem pons, solitary nucleus (dorsal medulla), and ventral medulla. The pontine respiratory group has connections to the hypothalamus and cerebral cortex, has inspiratory and expiratory functions, and may be involved in establishing respiratory patterns. The medullary centers, and particularly the pre-Bötzinger region of the ventral respiratory group, appear to be essential for establishing respiratory rhythmicity.

Pathophysiology

Sleep and breathing disorders and representative studies in PWS can be classified as follows (modified from Nixon and Brouillette) [127]:

1. Abnormalities of daytime breathing
   (a) Restrictive lung disease [128]
   (b) Abnormal ventilatory response to hypercapnia and/or hypoxia [129]
2. Abnormalities of sleep and wakefulness
   (a) Excessive daytime sleepiness [4, 5, 130–136]
   (b) Disorders of REM sleep
      (i) Respiratory abnormalities during rapid eye movement (REM) sleep [133, 135, 137]
      (ii) Disordered timing of REM sleep [134, 135, 137, 138]
   (c) Abnormalities of arousal—reduced arousal during sleep in response to hypoxic or hypercapnic stimuli [139, 140]
   (d) Sleep-disordered breathing
      (i) Obstructive sleep apnea [141, 142]
      (ii) Alveolar hypoventilation [127]
      (iii) Decreased oxygen saturation [133, 134, 137]
      (iv) Reduced ventilatory response to hypoxia and/or hypercapnia [140, 142]

The etiology and PWS-specific occurrence of these respiratory disorders is controversial. For instance, some studies show a surprisingly low occurrence of sleep apnea in PWS [132–134].

The excessive daytime sleepiness bears some resemblance to narcolepsy, a multifactorial genetic condition characterized by excessive, disabling daytime sleepiness, cataplexy and sleep paralysis, and severe disturbances in REM sleep. However, the bulk of information suggests that PWS and narcolepsy are distinct [127]. In addition, non-PWS narcolepsy has not been associated with genes within the PWS locus.

A hypothalamic disturbance has been proposed as a common link for the observed disorders. However, as reviewed above, the major control of resting automatic respiration is at the brain stem level. Ablation of higher centers, including the hypothalamus and cortex, has minimal effect on resting respiration [143]. On the other hand, the hypothalamus is involved in adjusting respiration in response to hypoxia, hypercapnia, and other sensory input, modulating cortical and brain stem outputs to affect ventilation. The extent of this influence in humans is not completely defined. In lower species, the hypothalamic response to hypercapnia is mediated by GABA, which may be of interest since several nonimprinted GABA receptor subunit genes are in the PWS region of chromosome 15q. In rodents, disruption of *Ndn*, an imprinted gene within the PWS region, results in the deficiency of oxytocin and gonadotropin-releasing hormone neurons in the hypothalamus [82], which is of interest in relation to the observed deficiency of hypothalamic oxytocin neurons in human PWS [144], although CSF oxytocin levels are reported to be high in PWS [145], and the variable hypogonadotropic hypogonadism, as discussed in a previous section of this chapter. Disruption of *Ndn* in rodents also leads to a disorder of respiratory drive similar to that observed in PWS; this effect may be related to neuronal migration abnormalities, particularly involving the pre-Bötzinger complex [146, 147]. Respiratory and breathing disorders also occur in patients with Schaaf-Yang syndrome, a PWS-like condition due to mutation of the paternal copy of *MAGEL2*, an imprinted gene within the PWS-region of chromosome 15q11–13 [148, 149].

Obesity has been proposed as a possible mechanism for obstructive sleep apnea in PWS; although the data are variable [127, 150]. Obesity or, more specifically, overweight has also been postulated to contribute to restrictive lung disease in PWS, as has been described in morbidly overweight individuals without PWS [151]. However, data suggest that respiratory muscle hypotonia may be a more important contributory factor [127, 128], especially since respiratory problems can be observed without excess body weight, as in neonates with PWS.

Sleep and respiratory disorders similar to PWS have been described in individuals with non-PWS neuromuscular disorders [112, 152–155]. In myotonic dystrophy, a condition often compared to PWS, a decreased number of neurons in the medullary arcuate nucleus (a postulated brain stem respiratory control center) was observed in 3 individuals with hypoventilation, as compared with 5 with myotonic dystrophy without hypoventilation and 18 controls [156]. Although these data were interpreted to be consistent with a primary central respiratory defect in myotonic dystrophy, it may also be consistent with retrograde loss of neurons due to peripheral muscle degeneration, weakness, and disuse, a situation that may also theoretically occur in PWS. Central, obstructive, and combined apnea, similar to the apnea described in PWS, have been characterized in non-PWS individuals with neuromuscular disease-causing weakness of the respiratory musculature [112].

Individuals with neuromuscular disorders may also be more prone to respiratory compromise during usual physiologic reductions in accessory respiratory and upper airway muscle tone that occur during REM sleep [157], a sleep period that appears to be particularly affected in PWS. Additional upper airway problems in PWS, e.g., decreased airway diameter, thick oral secretions, and possible adeno-tonsillar hypertrophy [127, 142] may further compound this problem.

Finally, individuals with PWS are deficient in growth hormone and insulin-like growth factor-I (IGF-I), a growth hormone-dependent peptide. Both growth hormone and IGF-I have been directly or indirectly shown to be respiratory stimulants [158, 159]. Withdrawal of growth hormone therapy in adults with non-PWS GH deficiency has been associated with a shift from

obstructive to central apnea and an increase in slow-wave sleep time [160].

The consequences of respiratory disorders in PWS have not been well defined, although this category of disorder is the most commonly identified cause of demise. As with other disorders involving respiratory muscle weakness, a decreased ability to compensate during acute lung disease or hypermetabolic states may account for the relatively high occurrence of pneumonia- and fever-related mortality. The decreased respiratory capacity can also lead to hypertrophy and eventual failure of the right heart (cor pulmonale), another commonly specified cause of death in PWS.

Evaluation

The evaluation of respiratory and sleep disorders gained prominence due to reports of respiratory-related mortality in children with PWS who received GH treatment (see Chap. 7) [161, 162]. An initial review by the manufacturer of Genotropin®, the GH brand labeled for treatment of PWS, revealed seven cases, all of whom had evidence of respiratory compromise (five with pneumonia) either preceding or at the time of demise ("Prader-Willi Syndrome and Death," Pfizer Global Pharmaceuticals, October 2, 2003). This led to the placement of an additional label in the package insert on April 30, 2003, including the following advisory:

> Growth hormone is contraindicated in patients with Prader-Willi syndrome who…have severe respiratory impairment…Patients with Prader-Willi syndrome should be evaluated for upper airway obstruction before initiation of treatment with growth hormone. If during treatment with growth hormone patients show signs of upper airway obstruction (including onset of or increased snoring), treatment should be interrupted. All patients with Prader-Willi syndrome should be evaluated for sleep apnea and monitored if sleep apnea is suspected.

Subsequent and previous case reviews of individuals with PWS who were *not* treated with growth hormone demonstrated that respiratory disorders are the major cause of morbidity and mortality and revealed little evidence of GH treatment contributing to these conditions [163].

Most of the attention regarding respiratory disorders has focused on identification of obstructive sleep apnea (OSA). This is based largely on data in non-PWS populations showing an association of OSA with morbidity. A review [127] found that the reported prevalence of obstructive sleep apnea in PWS ranged from 0% to 100%; subsequent case series have continued to show high variability in prevalence estimates. Available data are limited by small sample sizes, biased sampling, and differences in screening and diagnostic criteria. Nonetheless, the overall impression is that a significant proportion of individuals with PWS will be diagnosed with OSA if tested, i.e., that PWS is itself a risk factor for OSA. However, it is currently unclear whether all individuals with PWS benefit from the knowledge of this diagnosis in the absence of associated morbidity.

Clinical screening for OSA has been proposed in both PWS and non-PWS patients to improve the diagnostic yield of testing and/or to provide a basis for treatment. Snoring is a relatively poor indicator of significant OSA in non-PWS populations, although correlations may be improved by consideration of snoring characteristics [164, 165]. However, the diagnostic sensitivity and specificity of snoring for morbidity-associated OSA (i.e., OSA associated with cardiac, neuropsychologic, or other sequelae) have not been conclusively demonstrated in either PWS or non-PWS populations. Snoring is dependent on both relaxation of the pharyngeal muscles and airflow; therefore, for individuals with PWS, pharyngeal hypotonia could theoretically increase the prevalence of snoring; hypotonia-related hypoventilation could decrease the occurrence of snoring even in the presence of OSA. Other proposed clinical indicators of significant morbidity-associated OSA, including obesity (or overweight), sleep history, and daytime somnolence, have not been validated in PWS and are controversial in non-PWS populations.

The "gold standard" for diagnosis of OSA is nocturnal polysomnography, commonly referred to as a "sleep study," in which various parameters (oxygen saturation, carbon dioxide content, brain wave activity, sleep/wake status) are monitored

during sleep. However, there is controversy over the interpretation of polysomnographic data that is only partly resolved by consensus criteria, and outcome-based normative data are not available. Polysomnography prior to surgery, particularly tonsillectomy/adenoidectomy, has been recommended for PWS and for children without PWS who have clinical evidence of adeno-tonsillar hypertrophy and OSA and may have some impact on surgical outcomes and monitoring [166]. Abbreviated polysomnography and inadequately validated alternate procedures such as sleep and/or activity monitors cannot be recommended in PWS. A longitudinal study of children with PWS treated with GH showed that the percentages of patients with elevated obstructive apnea hypopnea index and severe adeno-tonsillar hypertrophy were higher at 4 and 5 years of treatment as compared to pre-GH treatment but were not correlated with IGF-I levels; respiratory disturbance and central apnea indices decreased during treatment. The authors concluded that GH treatment is safe but that polysomnography and adeno-tonsillar exam should be considered.

In contrast to OSA and sleep studies, there has been little attention paid to routine pulmonary function testing in PWS, e.g., measurement of lung volumes, inspiratory and expiratory pressures, and oxygen and carbon dioxide while awake. Pulmonary function testing provides important measures of ventilatory capacity and respiratory muscle function, both of which are known to be abnormal in PWS. The relative lack of attention to such testing may, in part, be due to the usual need for active cooperation from the patient and consequent perceived difficulties with PWS. Modified pulmonary function testing data in children with PWS have been reported [128, 167].

Based on available evidence, it does not seem advisable to *routinely* test all individuals with PWS for OSA or pulmonary function abnormalities outside of a research protocol. A large proportion will be diagnosed with a respiratory abnormality regardless of symptomatology, and there are no data correlating the results of such testing with risks for morbidity or mortality. In the absence of this information, routine testing could cause undue cost and concern. Polysomnography and/or pulmonary function testing in PWS would appear to be most useful in two circumstances:

1. To assist with therapeutic planning for patients with definite, persistent evidence of clinically significant respiratory compromise or sleep disorder, e.g., hypertension, evidence of pulmonary hypertension, or cor pulmonale
2. To monitor therapies that may affect respiratory function, e.g., surgical treatments, continuous positive airway pressure (CPAP), and growth hormone

Once a decision has been made to proceed with testing, it may be reasonable to routinely obtain pulmonary function testing and to limit the performance of polysomnography to those individuals with clinical evidence of sleep-disordered breathing or excessive daytime sleepiness.

Treatment

Given the high probability of finding a respiratory or breathing abnormality in an individual with PWS and the potentially invasive nature of some treatment modalities, the decision to initiate treatment should be carefully considered, preferably in consultation with specialists in PWS and cardiorespiratory care. Among the points to be considered are the following:

1. The indications for the evaluation, e.g., the signs and symptoms that prompted testing. If the testing was routine and the patient is asymptomatic, is treatment indicated? Or is continued monitoring preferable?
2. The feasibility and efficacy of treatment options. In most cases, this will be based on the consultant's own knowledge and experience, limited published data in PWS, and a larger published experience in non-PWS populations (which may or may not be directly relevant).
3. Overall clinical status and expected benefits for the individual patient.

Evaluation and treatment of contributory comorbidities should be first and foremost, even

in individuals with PWS who do not have documented respiratory abnormalities. Exercise and physical therapy may help improve respiratory and general muscle tone, thereby improving ventilatory effort. Exercise and weight control may also reduce the restrictive component of respiratory impairment [168–171]. Bracing and, if indicated, surgical correction of significant scoliosis may improve pulmonary function, particularly if the curvature is severe.

In non-PWS individuals with OSA, particularly those with evidence of tonsillar hypertrophy, adenotonsillectomy has been reported to improve respiratory status, although benefits over nonsurgical management may be modest [172]. There is limited published experience with adenotonsillectomy and a related procedure, uvulopalatopharyngoplasty, in PWS [127, 173, 174], and concerns have been raised regarding anesthesia and surgical risks, particularly in PWS [175].

Nasal mask or cannula delivery of oxygen and/or ventilatory support via continuous positive airway pressure or intermittent positive pressure ventilation, usually as a nocturnal therapy, may be beneficial in patients with chronic hypoxemia, although patient cooperation can be problematic [127, 131, 176].

Central respiratory stimulants, such as medroxyprogesterone, caffeine, and theophylline, have not been adequately studied in PWS and could have adverse effects on behavior. Modafinil and armodafinil, used for the treatment of narcolepsy and OSA, have not been studied in PWS.

Finally, growth hormone treatment has been associated with significant improvements in pulmonary function, including resting ventilation, airway occlusion pressure, and ventilatory response to carbon dioxide in children with PWS [167, 177].

Cardiovascular and Cerebrovascular Systems

Congenital cardiac, vascular, or cerebrovascular malformations and disorders have not been reported to occur with increased frequency, and there appears to be a surprisingly low occurrence in PWS in view of the obesity/overweight. These observations could be related to the unusual body fat distribution and the unexpectedly low occurrence of hyperinsulinemia.

Cor Pulmonale

Cor pulmonale (from Latin: *heart of the lungs*) can be generally defined as right heart dysfunction resulting from pulmonary disease. This condition is the most commonly reported cardiovascular complication in PWS and is often cited as a cause of mortality although careful examination of the literature reveals few well-documented cases.

Clinical criteria for cor pulmonale have been controversial. Weitzenblum [178] proposed that cor pulmonale be defined as "pulmonary arterial hypertension resulting from diseases affecting the structure and/or the function of the lungs; pulmonary arterial hypertension results in right ventricular enlargement (hypertrophy or dilatation) and may lead with time to right heart failure." A consensus panel sponsored by the World Health Organization [179] lists five categories of pulmonary hypertension. Categories 1 (pulmonary arterial hypertension), 2 (pulmonary venous hypertension), 4 (caused by chronic thrombotic and/or embolic disease), and 5 (caused by disorders directly affecting the pulmonary vasculature) do not appear to be relevant to PWS.

Category 3 is defined as "pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia." Eight subcategories are included: 3.1 chronic obstructive pulmonary disease, 3.2 interstitial lung disease, 3.3 sleep-disordered breathing, 3.4 alveolar hypoventilation disorders, 3.5 chronic exposure to high altitude, 3.6 neonatal lung disease, 3.7 alveolar capillary dysplasia, and 3.8 other. As described in the preceding section, categories 3.1, 3.3, and 3.4 are the most relevant to PWS.

Significant pulmonary hypertension is caused by *chronic* alveolar hypoxemia (PaO_2 <55–60 mmHg), as may occur with neuromuscular disease and resultant hypoventilation or with severe obstructive apnea. Alveolar hypoxemia causes pulmonary vasoconstriction, a normal

physiologic response. When this occurs chronically over a long period of time, it can lead to structural remodeling of the pulmonary vasculature and chronic pulmonary hypertension. The increased pressure causes resistance to the outflow of the right heart ventricle, leading to right heart hypertrophy or dilatation, with a risk for eventual cardiac failure. In non-PWS populations, chronic obstructive sleep apnea can be associated with a 17% to 41% occurrence of pulmonary hypertension. It has been stated that in this group of patients without intrinsic lung disease, pulmonary hypertension is rarely observed in the absence of daytime (awake) hypoxemia [180].

In non-PWS patients, clinical signs and noninvasive testing for pulmonary hypertension are considered to have variable specificity (i.e., indicative of the disorder if present) and relatively low sensitivity (does not rule out pulmonary hypertension if not present) and are usually seen late in the course of disease [178]. These findings include peripheral edema (especially ankle edema), a typical tricuspid regurgitation murmur, accentuation of the second heart sound, electrocardiogram evidence for right ventricular hypertrophy, and increased diameter of the pulmonary artery on chest X-ray. Echocardiographic methods are considered to be the best noninvasive tests for pulmonary hypertension and right heart status, correlating relatively well with more invasive methods. Magnetic resonance imaging (MRI) and other methods may provide additional information.

The treatment of pulmonary hypertension and, particularly, cor pulmonale involves (1) provision of oxygen to prevent pulmonary hypoxemia and vasoconstriction and (2) vasodilators. Surgical intervention may be necessary in severe cases. Evaluation and treatment of these disorders are best handled by an experienced cardiologist.

The occurrence of pulmonary hypertension, with or without right heart dysfunction, in PWS is not known. In a nationwide Danish study involving 155 individuals with PWS, no cases of pulmonary hypertension were identified [181]. However, since cor pulmonale appears to be a frequently reported cause of mortality in adults with PWS, a recommendation could be made for routine cardiac evaluation of adults with PWS who have risk factors for this condition.

Other Vascular Conditions

A few well-documented cases of coronary artery disease have been reported in PWS [182, 183]. Systematic investigation of biochemical risk markers for atherosclerotic heart disease have not been reported in PWS. As with ischemic heart disease, there are only scattered reports of cerebrovascular accident (stroke) in PWS. A case of apparent vaso-occlusive stroke with consequent moyamoya syndrome (revascularization of the middle cerebral arteries) was reported in a teenager with PWS and type 2 diabetes mellitus [184]. Since ischemic vascular disease is commonly linked to obesity and sleep-disordered breathing in the general population, the low prevalence of these conditions in PWS is surprising and may be due to the lower-than-expected occurrence of dyslipidemia and insulin resistance.

An increased occurrence of thromboembolic disease, including venous thrombosis and pulmonary embolism, has been reported in PWS [181, 185].

Miscellaneous Medical Concerns

Thermoregulatory Disorders, Autonomic Dysfunction, and Anesthesia Risk

The ability to maintain core body temperature within a narrow range is a major characteristic of normal mammalian physiology. Ambient (environmental) temperature sensation occurs via peripheral nerves that signal to a hypothalamic regulatory center, resulting in appropriate signaling back to the periphery through the autonomic and sympathetic nervous systems. A similar mechanism may be triggered with exposure to endogenous pyrogens (i.e., with febrile illness), although body temperature may be less efficiently regulated in these conditions.

During the usual resting state, body temperature (36.5°C) is higher than in the environment

(~25°C); the temperature difference is largely accounted for by heat generation resulting from routine metabolic processes. During ambient temperature fluctuations, both voluntary behavioral reactions (e.g., clothing and activity) and physiologic mechanisms are important elements of thermoregulation. When ambient temperature rises, the body dissipates heat via (1) vasodilation, which increases environmental heat exchange via radiation and convection (~75% of heat loss), and (2) sweating with evaporative cooling (~25%). When ambient temperature falls, the thermogenic response includes (1) norepinephrine-stimulated vasoconstriction, leading to decreased transfer of core body heat to the skin, and (2) shivering thermogenesis, in which there is progressive recruitment of muscle fibers that undergo involuntary, rhythmic contractions resulting in heat generation. Muscle thermogenesis can be further augmented by voluntary physical exertion; however, prolonged cold exposure and exertion can lead to fatigue and declines in both exertional and shivering thermogenesis. In small mammals and human infants, non-shivering thermogenesis from brown fat is a crucial mechanism for thermoregulation; however, this mechanism appears to be minimally active in human adults.

Clinically, thermoregulatory disorders can be defined as (1) an inability to normally regulate core body temperature in response to environmental temperature fluctuations, (2) extreme high fevers during illness, and/or (3) risk for hypo- or hyperthermia during anesthesia.

In a compilation of cases used for derivation of clinical diagnostic criteria for PWS, "abnormal temperature sensitivity" was reported in 3 of 65 (4.6%) individuals with PWS and none of 11 non-PWS individuals; this feature was included as a "supportive finding" for clinical diagnosis of PWS [29]. A survey study of 85 children with PWS found an increased occurrence of febrile convulsions and hypothermia (temperature less than 94°F) as compared with 85 non-PWS siblings and 118 well children [186]; however, there were no differences from a group of 105 non-PWS neurodevelopmentally impaired children. Hypothermia (rectal temperature 30°C) with complete recovery has been reported in a 5-month-old infant with PWS who may have been exposed to a very low ambient temperature [187]. Hyperthermia during illness was also postulated to contribute to mortality in several infants with PWS, possibly due to increased respiratory demand and compromise [12]. Together, these reports suggest but do not confirm a possible risk for temperature dysregulation in children with PWS.

A cold-exposure study was conducted in six PWS subjects and three non-PWS individuals placed into a cold room with temperature set at 4°C with light clothing for 1 hour [13]. Rectal (core) temperatures were noted to rise in all three non-PWS and two PWS individuals. Rectal temperature showed a small decrease in three of six PWS subjects, implying a defect in cold adaptation.

Temperature dysregulation has also been reported in a 37-year-old woman with PWS who had three separate episodes of hypothermia (27°C–32°C) associated with infections [188]. The risk for hypothermia was attributed to the use of risperidone, a dopamine and serotonin type 2 receptor antagonist. Hypothermia resolved after cessation of risperidone but recurred with the use of olanzapine, a similar medication. Hypothermia has also been reported with these medications in non-PWS individuals and with other psychotropic medications that are often used in PWS [189]; therefore, it is not clear whether the risk is greater for individuals with PWS.

Autonomic dysfunction has been proposed as a mechanism for the possible disorders of thermoregulation in PWS. The autonomic nervous system regulates smooth muscle, exocrine glands, and cardiac muscle and is largely responsible for maintaining somatic homeostasis through involuntary mechanisms. This is distinguished from the somatic motor system, which is responsible for primarily voluntary control of skeletal muscles. The hypothalamus is considered the control center for the autonomic system; however, multiple areas of the cerebral cortex, brain stem, cerebellum, and spinal cord also play roles. The autonomic system is divided into the sympathetic and parasympathetic systems. The sympathetic system arises from spinal cord neurons, giving

rise to segmental innervation of smooth muscle in the eye, heart, GI tract, and reproductive organs. The parasympathetic system arises from both brain stem neurons, including cranial nerves III, VII, IX, and X (vagus nerve) and sacral neurons, and is largely responsible for peristalsis and exocrine secretion.

Evidence for a generalized autonomic (parasympathetic) dysfunction was found in a study of 14 subjects with PWS (4–40 years old, 8 female) with a comparison group of individuals without PWS [190]. Within the PWS cohort, 50% had abnormal pupillary constriction to pilocarpine, and, on EKG, 6 of 14 had an abnormal ratio of the 30th to 15th R-R interval. A higher resting pulse and lower orthostatic pulse response was correlated with body mass index (BMI). Decreased frequency of respiratory sinus arrhythmia was also reported [191]. A later study in 32 individuals with PWS in a thermoneutral environment (72°F) was interpreted to show that resting cutaneous temperature and capillary blood flow were not different from controls, thereby supporting a theory of central as opposed to peripheral autonomic dysfunction [192], although the data showed higher capillary blood flow and mean cutaneous temperature in the group with uniparental disomy (n = 9) as compared with the deletion cases (n = 23) and controls (n = 5). Contrary to these findings, a detailed study in 26 individuals with PWS showed no differences in autonomic regulation of cardiac function as compared with age-, gender-, and BMI-matched controls [193].

Deficient sweating in response to environmental warming has been anecdotally mentioned as evidence for thermoregulatory and autonomic dysfunction in PWS. However, there are no published studies characterizing this condition. Other potential evidence for autonomic dysfunction include the decreased ability to vomit and decreased salivation, although there may be other mechanism for both of these characteristics of PWS.

Therefore, there is no current evidence that autonomic dysfunction accounts for thermoregulatory defects in PWS. In view of the normal physiologic dependence on shivering thermogenesis during exposure to cold, a risk for core hypothermia may be related to the decreased muscle mass.

Disordered thermoregulation during general anesthesia has also been raised as a concern in PWS, particularly the risk for malignant hyperthermia. This anecdotal concern arises in part from the increased risk for malignant hyperthermia observed in congenital myopathies, such as congenital myotonia and muscular dystrophy. Malignant hyperthermia is an autosomal dominant condition caused by a genetic disorder of calcium transport in skeletal muscle, leading to increased intracellular calcium, uncoupling of mitochondrial oxidative phosphorylation, and excess heat production to several times greater than normal [194]. Clinically, the condition may be triggered by several general anesthetic agents and muscle relaxants and is initially characterized by muscle rigidity, hyperthermia, and acidosis. To date, there are no documented reports of malignant hyperthermia or defects of muscle calcium transport in PWS.

A similar but pathologically unrelated condition, neuroleptic malignant syndrome, has been reported as an idiosyncratic reaction to a variety of psychotropic agents [195], including several that are often prescribed in PWS. These agents are thought to trigger an inappropriate hypothalamic response by inhibiting dopamine or enhancing serotonin action, leading to muscle rigidity and hyperthermia. In addition, the use of serotonin reuptake inhibitors, particularly in combination with other agents affecting serotonin action, has been associated with “serotonin syndrome” in non-PWS individuals [196]. Serotonin syndrome is characterized by hyperreflexia, tremor, muscle rigidity, autonomic dysfunction, mental confusion, and variable occurrence of hyperthermia, resulting from the muscle contractions. There are no published reports of either neuroleptic malignant syndrome or serotonin syndrome in PWS, despite the widespread use of potential triggering agents.

Finally, there have been no reports of postanesthetic shivering in PWS. In non-PWS patients, this condition is thought to be due to inhibition of thermoregulation by general anesthetic agents [197].

Limited case series and single case reports of children with PWS undergoing general or regional anesthesia showed no syndrome-specific complications [198, 199]; there are fewer published reports in adults with PWS. Individual cases may present challenges in relation to obesity, hypotonia, and airway access.

In summary, clinical experience suggests that a proportion of individuals with PWS may be at risk for thermoregulatory disorders, particularly environment-related hypothermia, which could be related to a diminished capacity for shivering thermogenesis. A clinically significant risk for temperature dysregulation may be particularly noted for infants with PWS, who may be prone to both hyperthermia with illness and hypothermia with environmental cold exposure. Unfortunately, however, there are insufficient data to answer the question of whether specific thermoregulatory abnormalities are more common in PWS and no conclusive proof of autonomic dysfunction. In addition, there are no data to indicate an increased risk for malignant hyperthermia, neuroleptic malignant syndrome, or serotonin syndrome. Nevertheless, in view of the relative paucity of published data and the potentially serious nature of these conditions, practitioners should be aware of the possible risks when confronted with specific situations.

Ophthalmologic Disorders

Esotropia has been reported in 43% of 15 infants and 66% of 65 older individuals with PWS and was included as a supportive finding for clinical diagnosis [29]. However, there are surprisingly few published studies characterizing ocular abnormalities and their treatment in PWS, and documentation of ophthalmologic findings is lacking in many descriptive series of the syndrome.

Esotropia is a type of strabismus (dysconjugate eye movement) in which one eye turns inward (toward the nose) while the other is fixated in a forward gaze. In a series of 46 patients clinically diagnosed with PWS, 22 were found to have esotropia, while 7 had exotropia or outward turning of the eye [200]. Additional defects included myopia (15%), significant astigmatism (oblong deformation of the eye leading to blurred vision, 41%), amblyopia (decreased visual acuity in one eye, 24%), and iris transillumination defects (33%). In a detailed study of 12 patients with PWS, Roy et al. [201] found only one patient with esotropia, two with exotropia, and nine with orthophoria (normal conjugate eye movements). One patient had myopic chorioretinal degeneration, one had disc atrophy and foveal hypoplasia, and five (42%) were noted to have telecanthus (increased distance between the inner corners of the eyes without orbit displacement).

Fox et al. [202] compared 20 PWS patients with deletion and 7 with uniparental maternal disomy with 16 controls matched for age, body composition, and intelligence. Strabismus was found in six deletion subjects (30%), four disomy subjects (57%), and four controls (25%); there were no significant differences between groups. Abnormal iris transillumination was found in four deletion and none of the disomy or control subjects. Foveal hypoplasia was not identified in any of the groups, while findings of astigmatism, amblyopia, and anisometropia were not significantly different between the PWS and control groups. Stereopsis differed ($p < 0.002$) between the PWS (45% deletion, 43% disomy) and controls (81%), indicating an increased defect in 3D perception in the PWS group. The mean level of myopia was also different ($p = 0.01$) between control (refractive error -2.33 ± 1.65SD) and PWS (-5.56 ± 5.38) subjects.

Ocular hypopigmentation has also been noted in PWS [203–205]. Generalized skin hypopigmentation is a well-known feature of PWS (~50% of cases) and may be associated with deletion of the *P* (pink-eyed dilution) gene, a nonimprinted gene located within the PWS deletion boundaries [206]. Mutations of the *P* gene are the cause of oculocutaneous albinism type 2 (OCA2) in humans, in which there is hypopigmentation of the eyes, skin, and hair. Associated findings include strabismus, loss of stereopsis, nystagmus, and foveal hypoplasia, apparently due to abnormal routing of the optic nerve pathways. The similarity of these eye findings along with

skin hypopigmentation to features of PWS suggested a similar pathogenesis. An initial study of six individuals with PWS and strabismus found abnormal visual-evoked potentials (VEP) in three of four hypopigmented patients and in neither of the two non-hypopigmented individuals [207]. The VEP abnormality was indistinguishable from that observed in OCA2, suggesting a similar abnormality in optic nerve pathways in PWS. However, the presence of strabismus in those patients with normal VEP was unexplained, and subsequent studies failed to confirm these findings in other individuals with PWS [201, 205, 208].

Overall, the data suggest that strabismus, both esotropia and exotropia, is not uncommon in PWS and may be related to ocular muscle hypotonia. A variety of other ophthalmologic disorders may also be present, including ocular hypopigmentation. These disorders could be related to deletion of the *P* gene, which is also associated with skin hypopigmentation. However, this link is far from certain because misrouting of optic nerve pathways, such as observed in OCA2, has not been confirmed in PWS.

Evaluation and treatment of eye conditions in PWS require consultation with an experienced ophthalmologist.

Sensory Function and Dermatillomania

Decreased peripheral and deep pain sensation is a commonly reported feature of PWS and, in the authors' clinical experience, a definite characteristic of the condition. Decreased pain sensation has been reported in 18% of individuals with PWS, with other reports indicating decreased pinprick sensitivity and decreased dermal and epidermal innervation [33, 203]. In the formulation of diagnostic criteria for PWS, a high pain threshold was reported in 9% of 65 typical PWS, 9% of 11 atypical PWS, and 9% of 11 control subjects [29]. Easy bruising has also been anecdotally reported and could be partially related to the decreased ability to feel pain; no other contributory factors have been identified.

Detailed studies in five children with PWS showed normal tactile perception (stereognosis), normal sensory nerve conduction (normal myelinization), and a 50% reduction in sensory nerve action potentials [209]. These latter results suggest that decreased density of peripheral nerve fibers may at least partially account for the decreased pain sensation. Lucignani et al. [210] found a reduction in gamma-aminobutyric acid type A (GABA-A) receptors in areas of the cerebral cortex that are related to pain response in six young adults with PWS (all deletion). The GABA-A receptor is composed of several subunits, three of which are coded by nonimprinted genes in the PWS region of chromosome 15q.

In view of the decreased pain sensation, it is important for caretakers to be vigilant for signs of infection and injury that might otherwise be signaled by pain or discomfort. Acute or unexpected changes in behavior, mobility, or gait may warrant further investigation.

Skin picking, or dermatillomania, is commonly observed in children and adults with PWS and is considered to be a compulsive disorder [211–213]. Disruption of the *Ndn* gene (an imprinted gene in the human PWS locus) in mice leads to increased skin-scraping behavior [82], which may be analogous to the skin picking behavior in human PWS. Functional magnetic resonance imaging studies indicate that the skin picking in PWS may be due to an interoceptive disorder, specifically involving processing of pain signals [214]. Skin picking in PWS often starts with a predicate lesion, such as an insect bite, cut or scratch, or ulcer. Consequent compulsive picking can result in severe ulceration and infection [215].

N-acetylcysteine (NAC) is an amino which, among other actions, may increase extracellular glutamate levels in the nucleus accumbens, a forebrain region involved in cognition, particularly in relation to reward and reinforcement behavior. A 12-week, randomized, double-blind, controlled study of orally administered NAC in adults with skin picking showed a significant reduction in this behavior [216]. An open-label trial in children and adults with PWS suggested similar efficacy [217].

Mitochondrial DNA

The mitochondria are intracellular organelles that are ancestrally derived from bacteria and live in the mutually supportive environment of the host cells. Mitochondria-dependent metabolic pathways, involving electron transport and oxidative phosphorylation, are the major source of energy in human cells. Some of the proteins involved in these processes are coded in the mitochondrial DNA, while others are coded in the nuclear DNA of the cell, demonstrating an evolved symbiotic relationship. A variety of human disorders, primarily involving muscle and central nervous system abnormalities, have been associated with defects in these genes.

As of this writing, none of the genes involved in the Prader-Willi region of chromosome 15q have been associated with mitochondrial function or cell energetics. However, the similarities of the muscle hypotonia in PWS to some types of mitochondrial myopathy have raised suspicions that there may be a relationship. Thus far, three cases of mitochondrial myopathy have been identified in children with PWS. A 2-year-old child with PWS and mitochondrial myopathy (complex I/IV respiratory chain deficiency diagnosed by muscle biopsy) was reported to have had open-heart surgery for atrial septal defect under general anesthesia without complications [98]. Two cases of PWS (maternal uniparental disomy) with mitochondrial myopathy (complex I deficiency) were reported in an abstract [218]; the diagnosis of mitochondrial myopathy was apparently pursued because of the neonatal hypotonia and the delayed clinical suspicion of PWS. The authors concluded that the mitochondrial myopathy was "likely a secondary rather than a primary event." However, the co-occurrence of these two relatively uncommon conditions suggests the possibility of a common pathogenesis and a need for larger-scale screening studies. A case of fatal metabolic acidosis in an infant with PWS is also suggestive of mitochondrial DNA disease [219].

There has been recent interest in the relationship of coenzyme Q10 (CoQ10) and PWS. CoQ10 is a protein encoded by the nuclear, rather than mitochondrial, DNA that plays an essential role in mitochondrial and extramitochondrial electron transport, as well as a variety of other vital functions. Plasma CoQ10 levels were lower in 16 individuals with PWS as compared with nonobese controls, but the levels were not different from a group of obese individuals [220]. The authors postulated that the lower plasma CoQ10 levels were due to the lower muscle mass and decreased energy expenditure in PWS. In view of these latter data and a lack of studies showing treatment efficacy, CoQ10 is not currently recommended as a medical therapy for PWS.

Epilepsy

Epilepsy is defined as a disorder of the central nervous system that causes convulsions (seizures). The physical manifestations of epilepsy range from subtle changes in behavior to major episodes of generalized involuntary motor activity. Various environmental factors, including increased body temperature, may increase the propensity or threshold for generation of the abnormal electrical impulses in the brain that lead to seizures.

There have been occasional reports of epilepsy or seizures in individuals with PWS [221] and a suggestion that infants with PWS may be susceptible to febrile convulsions; however, several systematic population surveys have failed to mention epilepsy as a specific feature of PWS [6, 29, 103]. On the other hand, epilepsy is a well-characterized feature of Angelman syndrome [222] and is also associated with other chromosome 15q11–q13 defects, including interstitial duplications of maternal origin within the PWS region [223–225]. A study of children referred from general pediatrics and neurology clinics reported a history of febrile seizures in 18 of 40 individuals (45%) with PWS and deletion, as compared with 1 of 14 patients (7%) with maternal uniparental disomy [226]. The same group reported seizures in 42 of 47 patients (89%) with Angelman syndrome and deletion, as compared with 4 of 9 patients (44%) with paternal uniparental disomy [227]. As noted by the authors, these results suggest that a lowering of the seizure

threshold, leading to a risk for febrile seizures in PWS and all seizures in Angelman syndrome, could be due to haploinsufficiency of a nonimprinted seizure-related gene, such as those that code for subunits of the gamma-aminobutyric acid receptor.

Cancer

Concerns have been raised regarding the possible association of PWS with increased risk for cancer. In 1985, Hall [228] published three cases of leukemia in individuals with PWS. No additional cases were presented until 1999, when Cassidy et al. [229] reported results from a survey study of the PWSA (USA) membership. Of 1077 valid responses (from 1852 members surveyed), there were 32 confirmed cases of cancer, of which 19 were benign; 3 of 53 deaths were attributed to cancer. Eight cases involved cancer types that are monitored by the Surveillance, Epidemiology, and End Results (SEER) Program, a project of the US National Cancer Institute, including three myeloid leukemia (one acute, two chronic, probably the same cases previously published by Hall). Other SEER-listed tumors in PWS included single cases of seminoma, dermatofibrosarcoma, ovarian teratoma, Hodgkin's lymphoma, and cardiac lymphoma. The eight observed cases were compared with the calculated expected number of 4.8 (based on data from SEER), indicating that there may be an increased overall occurrence of cancer in PWS.

Other cases of cancer reported in PWS include single cases of Wilms tumor [230], poorly differentiated hepatoblastoma in a 16-month-old boy (deletion 15q) [231], hepatocyte adenoma in an 11-year-old girl with known hepatic steatosis (fatty liver) [232], "pseudo-Kaposi" sarcoma in a 25-year-old male [233], testicular germ cell tumor [57], seminoma [56], acute lymphoblastic leukemia in a 14-year-old treated with GH [234], medulloblastoma [235], and a case of multiple endocrine neoplasia type 1 (MEN 1) [236]. A case of myelodysplastic syndrome in a 15-year-old boy with PWS was treated with allogeneic stem cell transplant [237].

Abnormalities of chromosome 15q, which is the location of the PWS region, are frequently found in tumor tissues from patients without PWS. Such tumors include breast cancers, bladder carcinoma, lymphoblastic leukemia, and particularly, myeloid leukemia [238, 239]. The reported 15q abnormalities identified in these conditions have included deletions, translocations, loss of heterozygosity, and duplications. The relevance of these findings to PWS is currently unknown.

Infections

Individuals with PWS may be prone to a variety of infections. However, any increased risk of infection appears to be primarily related to other characteristics of the syndrome. Primary immunodeficiency disorders have not been reported in PWS.

As described in previous sections, respiratory infections are a frequent cause of morbidity and mortality in PWS. The risk for serious respiratory infection is probably due to hypotonia of the respiratory musculature and consequent poor ventilatory capacity and reserve rather than inherent susceptibility to particular pathogenic organisms. Given the known risks for respiratory decompensation, judicious use of antibiotics should be considered if there is evidence of infection, even if a specific agent cannot be identified.

Dental infections are also common, as described in the next chapter, and are likely related to defects in salivation, high intake of sugar, and poor hygiene.

Skin infections are frequently observed in PWS. Contributory factors include obsessive skin picking (discussed elsewhere in this text) and decreased pain sensation, allowing traumatic skin injuries to progress to infection. All individuals with PWS should be examined regularly for cutaneous infections, particularly at pressure points (feet, buttocks) and in less-visible areas (scalp, perianal area, groin, axillae). In most cases, infected lesions can be successfully managed with topical antisepsis and topical or oral antibiotics. Culture and sensitivity studies should

be considered for persistent or unusual infections, and attention should be given to infectious agents endemic to the community, such as methicillin-resistant *Staphylococcus aureus*. Finally, the presence of systemic symptoms or acute onset of unusual behavior, body temperature instability, respiratory compromise, or uncharacteristic body movements may signal the presence of a deep tissue or systemic infection, such as osteomyelitis or pneumonia.

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6 Gastrointestinal System, Obesity, and Body Composition

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Obesity or increased body fat is arguably the most characteristic physical feature of Prader-Willi syndrome (PWS). Perhaps for this reason, a vast majority of the publications regarding PWS mention, discuss, and/or explore the topic of obesity. Despite this attention, the diagnosis, pathogenesis, optimal treatment, monitoring, and outcome of this condition in PWS remain controversial and incompletely defined. The paradox of the underweight infant with PWS evolving into an overweight child and adult has led to considerable speculation regarding pathophysiology. In addition, there is an inappropriate interchangeable use of the terms obesity, body mass index (BMI), and weight in the medical and scientific literature.

In addition to obesity, which is related to nutrition and intermediary metabolism, a variety of gastrointestinal (GI) disorders have been identified in PWS. A description of the GI system and related disorders in PWS will start this chapter, followed by a discussion of obesity and related nutrition and medical issues. Finally, a discussion of analytical methods for body composition analysis and their application in PWS is presented.

Gastrointestinal System and Disorders

The primary function of the gastrointestinal system is to facilitate ingestion, digestion, and absorption of fluid and nutrients. The anatomic elements of the system and their functions are as follows:

1. Oropharynx and esophagus: sucking, mastication (chewing and softening of food), salivation, swallowing (deglutition), and transfer of food to the stomach
2. Stomach, pancreas, and intestines: digestion, production of regulatory hormones, absorption of nutrients, and elimination of waste

Elements of these processes may be relevant to the pathophysiology of PWS. Therefore, each of the following sections begins with a brief description of the relevant physiology, followed by a review of PWS-related pathophysiology and treatment.

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Oropharyngeal Physiology

Non-PWS

The oral cavity undergoes continual involuntary salivation and swallowing, especially in the resting state in which a person is not eating or vocalizing. Saliva is derived primarily from the parotid, submandibular, and sublingual glands in the oral cavity (90%); another 10% is derived from scattered salivary glands; an average adult produces 0.5 to 1.5 L per day. Saliva is composed primarily of water with dissolved proteins, enzymes, and minerals; the composition differs according to the source gland and other factors. The major functions of saliva include lubrication and cleansing of the oral cavity, neutralization of acids, inhibition of microbial growth, and protection of dentition [1, 2].

Taste, smell, and palatability are among the initial food qualities that determine intake and retention of substances in the oral cavity. After entry of solid or semisolid food into the oral cavity, a complex neuromuscular process of chewing (mastication), salivation, and swallowing (deglutition) follows. Ingestion of fluid primarily involves deglutition without mastication.

Mastication combines a number of processes, including reduction of food to smaller pieces suitable for deglutition [3]. Teeth serve as passive tools for this process and are controlled by coordinated activity of the jaw muscles. The tongue participates in churning and mixing of food in the oral cavity and movement of food toward the oropharynx. Coordinated movement of the jaw, laryngeal, and pharyngeal muscles occurs both voluntarily and involuntarily, with neurosensory input and feedback. Mastication may also have roles in food selection and feedback regulation of appetite, although this has yet to be definitively demonstrated in humans [4].

Increased salivation occurs in anticipation of food intake (e.g., via visual and olfactory inputs), during taste (gustatory stimulus), and during mastication [1]. Gustatory input via cranial nerves VII (facial), IX (glossopharyngeal), and X (vagus) and masticatory input via cranial nerve V (trigeminal) to the brainstem salivary center is then relayed back to the salivary glands via cranial nerves VII (to the submandibular and sublingual glands) and IX (to the parotid glands), resulting in increased salivation. The stimulated parotid gland, which produces an amylase-rich saliva, may account for 50% of total saliva production during mastication. During mastication, saliva has key roles in enhancing taste perception, solubilizing food products, initiation of starch and lipid digestion, and preparation of food boluses for swallowing.

The process of deglutition starts with movement of processed food toward the back of the oral cavity, accomplished primarily by voluntary movement of the tongue. The second stage involves a reflex elevation of the pharynx and peristaltic movement of the food into the esophagus. The larynx also elevates, with closure of the epiglottis, thereby protecting the airway during swallowing [5]. The final stage of swallowing involves anterograde esophageal peristalsis, resulting in movement of the food bolus and liquid into the stomach. Deglutition is mediated by input via cranial nerves IX and X to the brainstem swallowing center, with output via cranial nerves V, VII, IX, X, and XII [1, 6, 7]. The process is facilitated by saliva, which provides the necessary lubrication. In addition, saliva buffers the oropharynx and esophagus against acidic intake and back leakage of gastric acid.

The human neonate relies exclusively upon the suck reflex for nutrient ingestion [8, 9]. The suck reflex, which develops relatively early during fetal life, involves intra- and perioral stimulation leading to activation of brainstem centers interacting with the motor cortex, resulting in rhythmic motor activity mediated by cranial nerves V, VII, and XII. Nonnutritive sucking (e.g., use of a pacifier) may have somewhat different dynamics and regulation from nutritive sucking (i.e., breast- or bottle-feeding) [8], the latter involving additional coordination with deglutition. Although a sucking motor pattern can be identified in the 10- to 12-week human fetus, full coordination of sucking, swallowing, and respiration does not occur until after 35 weeks [10, 11]. As with food intake later in life, the suck reflex and deglutition of ingested liquid in the

fetus and infant is highly dependent upon oropharyngeal muscle tone and function.

Pathology in PWS

Generalized hypotonia in the neonate with PWS is manifested by an extremely weak suck reflex, lacking in both strength and endurance [12]. In addition, apparent lack of coordination between suck/swallow and breathing has been observed. Hypotonia of the laryngeal, pharyngeal, and esophageal musculature could lead to further problems with swallowing, airway protection, and efficient movement and retention of liquid in the stomach [13, 14]. Silent aspiration was observed in the majority of infants with PWS during a video-fluoroscopic swallow study [14].

Although the oropharyngeal hypotonia usually improves sufficiently to allow adequate oral nutrition by 6 to 12 months of age, the underlying problem probably continues throughout the life span. Older individuals with PWS avoid meat and other foods that require a relatively high oromotor effort, which may enhance the usual human preference for carbohydrates over protein [15]. Micrognathia and microdontia (small lower jaw and teeth), noted in some individuals with PWS, may further compound the problem by providing less muscle bulk and surface area. Hypotonia, inadequate mastication, and oromotor discoordination may contribute to an increase frequency of choking fatalities in older children and adults and PWS [16].

Also problematic is the lack of adequate salivation. Unusually viscous saliva has been noted in most individuals with PWS, and decreased volume of saliva is virtually universal [17]. Abnormally low salivary flow rate with increased concentrations of all measured solutes (including fluoride, calcium, phosphorus, chloride, sodium, and protein) has been demonstrated [18–21] A similar, but not entirely identical, condition of decreased salivation and hyper-concentration of salivary fluid has been noted in non-PWS patients with denervation of the parotid gland [22]. No anatomic salivary gland abnormalities have been identified in PWS; however, a possible role of a neuronal migration defect due to lack of *NDN* expression has been postulated [23].

Decreased salivary secretion, or xerostomia ("dry mouth"), leads to decreased natural cleansing of the oral cavity, dental caries, enamel erosion, infection, and tooth loss [18, 20, 24]. These disorders are similar to those observed with xerostomia associated with other conditions [25]. Enamel erosion is due to inadequate salivary buffering of food-derived acids from citrus, acidic substances (including carbonated sodas, both regular and diet), and bacterial metabolism of dietary sugar and starch, resulting in resorption of bone mineral in the acidic milieu.

In non-PWS patients, xerostomia has been associated with speech abnormalities (dysphonia), a sensation of thirst resulting in frequent sipping, oral discomfort, difficulty with mastication and swallowing, taste disturbances (dysgeusia), heartburn, and halitosis [1, 25]. Several of these features are also noted in individuals with PWS.

Treatment

In neonates with PWS, hypotonic suck and lack of a coordinated feeding mechanism can often lead to a severe failure-to-thrive. Nasogastric tube-feeding is often used to meet nutritional needs, and many infants require gastrostomy tube placement to facilitate feeding for the first few months of life.

The use of treatment strategies to improve oromotor strength and coordination of swallowing can significantly enhance feeding success [13]. Such strategies may include early introduction of occupational and speech therapies, use of adaptive devices, positioning strategies, jaw-strengthening exercises, thickening agents for liquids, and use of low-calorie binding agents. These therapies reduce the need for parenteral (tube) feedings, as shown by our experience at Texas Children's Hospital (Fig. 6.1). Infants with PWS who received supplemental oromotor therapy required nasogastric feedings for a mean of 40 days, as compared with 234 days for infants who did not receive this therapy ($p = 0.003$).

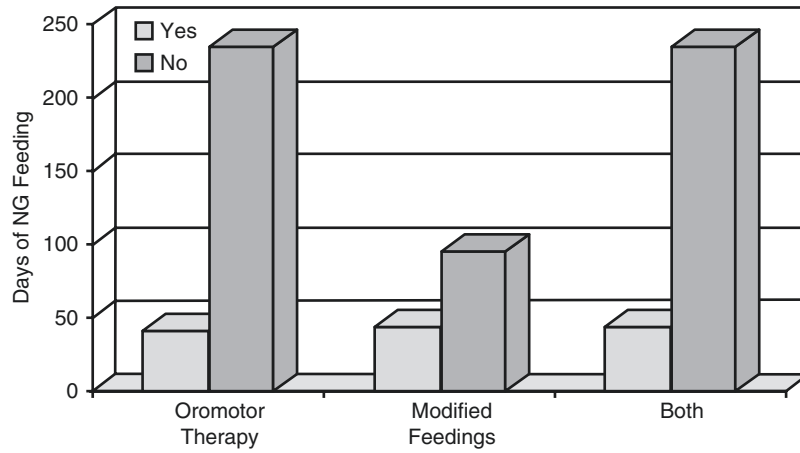

Fig. 6.1 Impact of supplemental therapies on the duration of nasogastric tube feedings in infants with PWS (total $N = 15$). The y-axis is the mean number of days that nasogastric feedings were required. The x-axis shows supplemental therapies that were administered. (*Source:* A. Scheimann, unpublished data; [26])

Occupational and speech therapy are recommended for individuals with PWS after the neonatal period to address the functional hypotonia and speech abnormalities. However, the efficacy of these treatments in relation to feeding behavior and food preferences has not been studied in PWS.

Treatment of xerostomia in non-PWS patients often involves the use of natural secretagogues (e.g., sour lozenges, sugarless chewing gum) to provide continuous salivary gland stimulation. This approach has been reported in some individuals with PWS [27]. Larger-scale studies have not been conducted. Pharmacologic treatment of xerostomia in non-PWS individuals may include artificial saliva and sialagogues, for example, pilocarpine and cevimeline. In addition, neuroelectro-stimulation is currently in development [28]. These treatments have not been formally studied in PWS.

Given the high risks for severe dental caries and infection, regular dental care must be established for all individuals with PWS [29]. Oral hygiene should be instituted in infancy even if dental eruption has not yet occurred, including use of soft foam toothbrushes and wetting solutions. This may be particularly important for infants on parenteral or gastrostomy feedings, where there is virtually no stimulation of salivation or wetting from oral feeds. Fluoride treatment may also be recommended. For treatment of caries, adhesive dental techniques have been recommended [30]. In some cases, orthodontic procedures can provide functional benefit [31].

Avoidance of sugars, thick starchy foods, citrus, carbonated drinks, and other acidic foods is advisable. In addition, individuals with PWS should be encouraged to drink adequate amounts of water with each meal to facilitate mastication, swallowing, and oral cleansing.

Stomach, Pancreas, and Intestines

Physiology

Following passage of food from the oropharynx to the esophagus, peristalsis results in delivery of food boluses into the antrum of the stomach. In the resting condition, the lower esophageal sphincter, composed of specialized smooth muscle cells (not a true sphincter), maintains a positive pressure to prevent gastric contents from moving back into the esophagus. During swallowing, this pressure is released in response to local stimuli, including vasoactive intestinal peptide (VIP) and nitric oxide, thereby allowing food to enter the antrum of the stomach.

The stomach, which begins at the lower esophageal sphincter and ends at the pyloric sphincter, is composed of inner circumferential and outer longitudinal layers of smooth muscle which undergo rhythmic contractions controlled by a pacemaker located in the main body of the stomach. The stomach is lined by secretory cells,

including parietal, chief, and mucus cells. In response to food-related stimuli (smell, visual, cerebral), the vagus nerve signals release of acid from the parietal cells; this effect is mediated by histamine and gastrin. The acid environment, in turn, inhibits further gastrin release and also stimulates local production of somatostatin, which inhibits histamine and gastrin release. The parietal cells also produce intrinsic factor, which is required for absorption of vitamin B_{12}.

Vagal stimulation also results in release of pepsinogen from the chief cells of the stomach. In the presence of gastric acid, pepsinogen is processed to pepsin, which is the major enzyme involved in the initial steps of protein digestion.

Neurons within the stomach produce a number of substances that participate in regulation of gastrin, histamine, acid, and somatostatin release. These include acetylcholine and calcitonin gene-related peptide from the vagus nerve, pituitary adenylate cyclase-activating peptide, VIP, gastrin-releasing peptide, galanin, and nitric oxide from enteric neurons. Some of these peptides are also postulated to affect normal eating behavior and are discussed in the section on obesity.

When liquid substances enter the stomach, vagal stimulation results in relaxation of the proximal stomach, where the liquid is retained until gastric emptying. Solid foods are mixed, digested, and reduced to small particles in the distal stomach. Gastric emptying is accomplished by both muscular contractions of the stomach and by alternate opening and closure of the pyloric sphincter, which is under sympathetic and vagal control, respectively.

After passing through the pyloric sphincter, partially digested material enters the duodenum, where the fat, protein, and gastric acid stimulate duodenal production of cholecystokinin (CCK) and secretin. These peptides are absorbed into the bloodstream and travel to the pancreas, activating vagal stimulation of pancreatic enzyme secretion into the intestinal lumen. Duodenal distention also leads to pancreatic enzyme secretion through direct vagal stimulation (enteropancreatic reflex). These enzymes include (1) pancreatic amylase, which digests carbohydrates to oligosaccharides; (2) lipase and colipase, which digest fat (triglycerides) to monoglycerides and fatty acids; and (3) trypsin, chymotrypsin, and elastase, which digest peptides (resulting from pepsin digestion of proteins in the stomach) to oligopeptides.

Further digestion into amino acids, fatty acids, monoglycerides, and monosaccharides occurs in the small intestine. These nutrients are absorbed into the bloodstream from the intestinal lumen. In addition, the small and large intestines are responsible for absorption of water and electrolytes. Finally, the large intestine and anal sphincter are responsible for the process of solid waste elimination, or defecation.

A number of peptides are released from the gastrointestinal tract and pancreas into the bloodstream during the process of food intake, digestion, and absorption. These include insulin, glucagon, and several peptides which are postulated to be appetite-regulatory hormones.

Pathology and Treatment in PWS

Retrograde movement of ingested substances Normally, ingested nutrients move in an anterograde (forward) fashion from the mouth to stomach to intestines with minimal backflow. Passive retrograde movement of food from the stomach into the esophagus (gastroesophageal reflux, GER) and oropharynx mouth (regurgitation) can occur, the latter sometimes accompanied by usually non-forceful spitting up. Forceful expulsion of stomach contents, or emesis, may occur via voluntary and involuntary (autonomic) processes. Voluntary regurgitation and reprocessing of food from the stomach, or rumination, may also occur. Retrograde movement of intestinal contents has been observed in cases of severe obstruction and constipation in patients without PWS, but these problems have not been reported to be a particular concern in PWS.

Regurgitation is a relatively common finding in otherwise normal (non-PWS) infants, clinically observed in most infants under 3 months of age and usually resolving within the first year of life [32, 33]. It has been postulated that reflux may trigger arousal, thereby being protective against sudden death in infants. The frequency

and severity of regurgitation may be increased in infants with hypotonia, prematurity, or other predisposing conditions. Contributory factors may include transient relaxation of the lower esophageal sphincter pressure and positioning after feeds. In addition, in non-PWS infants, it has been found that a nasogastric tube increases the frequency of reflux episodes [34].

In older non-PWS children and adults, GER with or without regurgitation may be associated with symptoms of "acid reflux" or heartburn. Endoscopic evaluation and surgical treatment may be necessary. In severe cases, chronic reflux of gastric acid can cause esophagitis, esophageal stricture, and cellular dysplasia and carcinoma of the distal esophagus.

GER and regurgitation have been occasionally reported in PWS, but systematic documentation of prevalence has not been performed. Anecdotal experience suggests that clinically significant regurgitation is not as commonly observed in infants with PWS as might be expected. This may be partly attributable to the lower volumes per oral feed that are usually ingested.

There are concerns regarding the possibility that due to hypotonia, infants with PWS may be unable to adequately protect the airway during reflux episodes, thereby increasing the risks for aspiration pneumonia and respiratory compromise. As a safety measure, reflux precautions should be taken for all infants with PWS, especially if taking substantial volumes of oral bolus feeds, and continued until the child is ambulatory. However, optimal precautions have not been defined in infants with PWS. In non-PWS infants, a 30-degree incline post feeds, for example, in an infant seat, had been traditionally recommended. Given the concerns that this may worsen reflux in some infants due to increased intra-abdominal pressure, left-lateral or upright (carried) position has been recommended. In any case, a supine position should be avoided.

Typical signs, symptoms, and complications due to GER with or without regurgitation have not been reported in older children and adults with PWS. Since individuals with PWS have decreased pain sensation (see Chap. 5), typical symptoms of heartburn may not be a reliable indicator of GER.

Emesis is an active process that may be considered a normal protective reflex. When emetic agents and toxins enter the gastrointestinal lumen, mucosal chemoreceptors are triggered which then signal through the vagus nerve back to a brainstem emetic center [35]. Emetic toxins in the bloodstream signal directly to this same area through the area postrema of the brainstem. Processing of these signals results in sequential signaling through vagal and other motor neurons, resulting in retching (simultaneous, forceful contractions of the diaphragm and abdominal muscles) and expulsion (prolonged forceful contraction of the abdominal muscles in coordination with the rib cage and pharyngeal and laryngeal muscles). Retrograde intestinal contraction occurs with gastric relaxation. Emesis then results from sequential and coordinated increases in intra-abdominal and intrathoracic pressure. Active retrograde peristalsis of the stomach or esophagus is not thought to be involved in emesis. Hypothalamic release of vasopressin and oxytocin may be involved in the emetic process.

A commonly reported feature of PWS is a decreased ability to vomit, with a complete absence of "natural" or induced (e.g., with ipecac) emesis noted in a large proportion of individuals [17, 36]. Hypotonia of the diaphragmatic, abdominal, and intercostal muscles may contribute to this deficiency since forceful contractions of these muscles are required for emesis. A deficiency of oxytocin neurons [37] could play a role, although CSF oxytocin levels are reported to be elevated in PWS [38]. Vagal autonomic dysfunction is also a possibility, although, as reviewed in Chap. 5, the evidence for autonomic dysfunction in PWS is limited.

Caution has been advised regarding reliance on emetic agents, particularly syrup of ipecac, in the treatment of accidental poisoning for individuals with PWS since the response may be inadequate. Since ipecac is no longer recommended for home treatment of poison ingestion; this issue may be a moot point. However, healthcare practitioners should be aware of the

decreased ability to vomit if an emetic therapy is considered in the emergency room or other medical care facility.

Some individuals with PWS may have rumination, a condition characterized by voluntary regurgitation of gastric contents that are then rechewed and re-swallowed. A survey study found that 10% to 17% of 313 individuals with PWS reported a history of rumination and that approximately half of this group had a history of emesis [36]. Rumination was also suspected in a 17-year-old with PWS who was found to have gastric secretions in her pharynx despite fasting during preparation for general anesthesia [39]. Rumination may be a form of self-stimulation and, in the case of PWS, a means of obtaining food, albeit reprocessed. Regurgitated stomach contents are usually acidic, which may add to the xerostomia-related risk for dental enamel erosion. Therefore, in addition to behavioral treatment, the use of pharmacologic agents to block stomach acid secretion should be considered in patients who have rumination.

Gastric dilatation In 1997, Wharton et al. [40] reported six females with PWS who suffered massive gastric dilatation; two died of gastric necrosis, one died of cardiac arrest, and three survived. Fever, abdominal pain, and distention were presenting signs, and vomiting was reported in two cases. These individuals had all had strict dietary control; the authors postulated that gastric muscular atony and atrophy may have occurred as a result of the dietary limitations, resulting in dilatation and necrosis following sudden ingestion of a large quantity of food. Additional cases have since been reported [41, 42]; however, the prevalence and etiology of this condition in PWS are unknown. Aside from the usual recommendations for prevention of binge eating, caretakers should be vigilant for signs of acute onset of unusual abdominal distention, fever, and emesis.

Bowel complaints As indicated in Fig. 6.2, complaints related to bowel function are frequently reported by individuals with PWS (data summarized from various sources).

The composite data indicate that 20% of individuals with PWS report constipation, and a recent study found constipation in 8 of 20 (40%) adult women with PWS [44]. Constipation can be defined as hard, dry stool, with bowel movements usually occurring less than three times a week. Abdominal and rectal pain, rectal fissures, hemorrhoids, and rectal bleeding (bright red blood) may occur. In addition, affected individuals may have abdominal distention, bloating, and a gen-

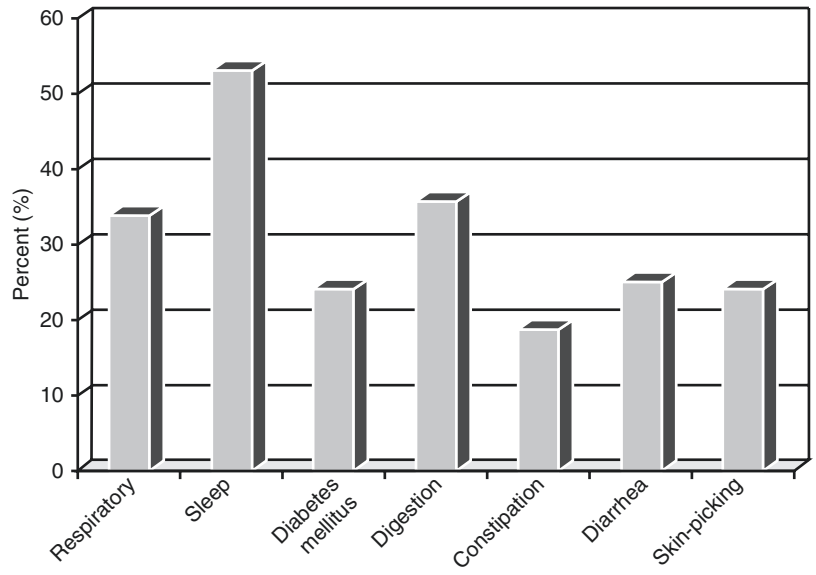

Fig. 6.2 Symptom prevalence in adults with PWS [17, 43]

eral feeling of discomfort. Lack of dietary fiber and inadequate liquid ingestion may be contributory factors. Hypotonia of the pelvic floor and abdominal muscles can hinder defecation. General physical immobility is also associated with constipation. Although hypothyroidism does not occur with increased frequency in PWS, it is a common condition in the general population and may present with constipation.

Treatment of constipation involves provision of adequate dietary water and fiber, encouragement of physical activity, and thyroid hormone replacement, if deficient. In some cases, rectal stimulation, irrigation, suppositories, or enemas may be necessary to clear the rectal ampulla. Defecation can be hindered by hypotonia; therefore, ensuring proper posture for toileting can be beneficial.

At present, there are no contraindications to laxative use aside from a relative concern with use of mineral oil due to the potential for aspiration. Polyethylene glycol can be used provided there is sufficient consumption of fluid within 20 to 30 minutes to allow the osmotic effects to occur. Magnesium-containing laxatives are another option for individuals with normal renal function.

Diarrhea, often thought of as the opposite of constipation, can be defined as loose, watery, and frequent stools. The composite data indicate that diarrhea is reported more frequently than constipation in PWS. Noninfectious diarrhea can be caused by consumption of large amounts of poorly absorbed dietary sweeteners (e.g., sorbitol or fructose) or fat substitutes (e.g., olestra), use of anti-absorptive agents (e.g., orlistat), and food intolerance (e.g., lactose intolerance). Consumption of contaminated foods, not uncommon in PWS due to the foraging behavior, enhances the likelihood of acquiring infectious diarrhea. In addition to a careful history, examination of the stool and a blood count; stool cultures, including cultures for *Clostridium difficile*; and parasite studies, including for *Giardia lamblia*, may be included in the evaluation, if clinically indicated.

Treatment of diarrhea is dependent upon the cause. It is also important to distinguish diarrhea from overflow incontinence due to stool impaction, a condition which will require treatment of the impaction and constipation.

Diarrhea, especially if copious, watery, and acidic, can cause perianal irritation, bleeding, and infection. These secondary conditions also require attention and treatment.

Rectal ulcers may occur because of a regional skin picking and is sometimes termed "rectal digging" [45–47]. This behavior is often exacerbated by rectal irritation from constipation, diarrhea, or large stools. Symptoms may include mucoid rectal discharge, bloody stools, constipation, rectal pain, abdominal pain, and tenesmus. Behavioral and medical treatment may be beneficial, including interventions to decrease the tendency for picking and to improve toilet posture. Wearing pajamas at night, such as onesie pajamas worn backward, and use of pelvic floor physical therapy can be useful adjuncts. Prevention and treatment of constipation are also recommended to avoid rectal irritation.

Other Gastrointestinal Organs

No intrinsic structural or functional abnormalities in pancreatic exocrine or endocrine function have been identified in PWS.

Nonalcoholic fatty liver disease (NAFLD) is a condition that typically occurs in obese individuals, particularly those with insulin resistance, and is characterized by lipid accumulation in the liver [48]. NAFLD may progress through the stages of fat accumulation (hepatic steatosis), fibrosis and inflammatory necrosis (nonalcoholic steatohepatitis), cirrhosis, and liver failure. The first stage is fairly common in the general obese population; subsequent progression is less common, but NAFLD is a major cause of nonalcoholic liver failure in the overall population. Diagnostic signs include elevated transaminase levels, liver enlargement, and ultrasound evidence of hepatic steatosis. Hepatic steatosis has been occasionally reported in cases of PWS; however, the overall prevalence may be lower than for non-PWS matched controls [49]. Treatment of obesity is a

primary clinical approach to treatment of NAFLD. The pharmacologic treatment of NAFLD has not yet been delineated, although metformin may be beneficial [50].

There have been two case reports of childhood liver tumor in PWS, an adenoma and a hepatoblastoma [51, 52] which may represent chance associations. Cholelithiasis has been occasionally reported in individuals with PWS, with clinical presentation including pain and jaundice [53].

Obesity

Definition and Diagnosis of Obesity

The term "obesity" is derived from the Latin term obesus, an adjective used to describe a condition of being corpulent. In medical terminology, obesity is defined as excessive body fat or an excess proportion of fat to nonfat mass independent of total body mass. Therefore, obesity is not synonymous with weight, although the two terms are often used interchangeably.

Total body mass or weight can be clinically deconstructed into fat mass and nonfat mass, the latter primarily composed of muscle and bone. In healthy individuals and in most human pathologic conditions, changes in weight result in simultaneous but nonparallel changes in both fat and fat-free or lean mass, a phenomenon which has been characterized as the "companionship of lean and fat" [54]. As individuals become obese, fat mass increases faster than lean mass. Conversely, during usual weight loss (e.g., calorie reduction), obese individuals will lose both fat and lean mass, but fat will decline at a faster rate. The dynamic relationships of fat or lean mass vs. total body mass are remarkably superimposable regardless of underlying condition, including in usual or exogenous obesity, diabetes mellitus, anorexia nervosa, and cystic fibrosis. A major identified exception is Prader-Willi syndrome, in which lean mass constitutes a significantly lower proportion of total mass [55]. Therefore, in individuals with PWS, there is an excessive proportion of fat to total body mass, or obesity, across the weight range, including in underweight infants [56–59]. Wasting associated with human immunodeficiency virus infection may be another exception to the companionship of lean and fat rule, with a decreased proportion of lean mass [60].

For population-based studies, the intrinsic relationships of fat and lean mass provide a rationale for using a modified ratio of weight to height for estimation of body fatness. In the 1970s, weight (kg) divided by height squared (m^2), also known as body mass index (BMI), was incorporated into the National Health and Nutrition Examination Survey by the US Centers for Disease Control (CDC) as a measure of obesity in the population. However, it should be remembered that despite the widespread use of BMI in clinical medicine, this measure was never intended to diagnose obesity in individual patients. In fact, the CDC website page for BMI (cdc.gov) currently includes this caveat: "BMI can be used to screen for weight categories that may lead to health problems but it is not diagnostic of the body fatness or health of an individual."

For individual non-PWS patients, physical examination including anthropometric measurements is the first step in the clinical diagnosis of obesity. More precise tools exist for estimation of percent body fat, as detailed in later sections of this chapter. In patients with PWS, visual inspection and waist circumference may grossly underestimate body fat. An individual with PWS who appears obese by clinical judgment will be considerably more obese than a non-PWS individual with similar weight (or BMI) and appearance. Therefore, in the natural history of PWS, while a high BMI invariably equates to obesity, lower levels are also accompanied by increased body fat or obesity; that is, all individuals with PWS, regardless of weight, are obese. Distinguishing obesity and BMI may be important in terms of defining related morbidity risks and treatment.

Pathogenesis

Given the above consideration, the pathophysiology of obesity in PWS can be separated into two potentially inter-related questions: (1) What causes the apparent violation of the "companionship rule," that is, why is the fat-to-lean mass ratio abnormally high, independent of weight? (2) What causes the apparently insatiable appetite and the consequent unlimited weight (primarily fat) gain? In addition, there is the question of whether obesity in individual with PWS carries the same risks for morbidity as in non-PWS individual. Answers to these questions are crucial to understanding the pathogenesis and appropriate treatment of obesity in PWS.

The inappropriate proportion of fat to nonfat mass in individuals with PWS probably begins in utero and is accompanied by an absolute deficit in muscle mass. This could result from either (1) inappropriate preferential shuttling of nutrients into fat, thereby causing a deficit in lean mass, and/or (2) inappropriately low utilization of nutrients by muscle, leading to a default deposition of fat.

The mechanisms by which the human body shuttles ingested substrate (glucose, amino acids, fatty acids) into fat, muscle, and bone have not been completely defined, and a discussion of this topic is beyond the scope of this chapter. There is evidence that hormones and neuropeptides that may regulate appetite (e.g., leptin, neuropeptide Y (NPY), adiponectin, agouti-related protein) may also affect substrate partitioning; however, much of the data has been collected in rodents and may not apply directly to humans. In addition, no specific defects in the physiology or action of these substances have been reported in PWS, and none are coded within the PWS gene region. Therefore, it is not known at this time whether the primary body composition abnormality in PWS is excess lipogenesis, decreased formation of muscle, or a concomitant dysregulation of both fat and nonfat mass accretion.

The propensity for insatiable appetite and weight gain in PWS is likewise not completely understood. Normal eating behavior has been separated into three components: (1) an initial, relatively acute "drive to eat," or hunger; (2) an immediate postmeal feeling of fullness, or satiation; and (3) a longer-lasting feeling of satisfaction, or satiety. The regulation of each of these stages is likely to be different. On a theoretical basis, extrinsic factors, for example, environmental stimuli, may have a relatively higher impact on hunger, whereas satiety and satiation may be more dependent on intrinsic physiology. A detailed study of eating behavior in PWS indicates that the primary deficit involves satiation rather than hunger [61] although satiety was not distinguished from satiation. Other studies are consistent with a defect in satiety [62].

Studies in non-PWS individuals have shown a relationship of higher fasting gastric volume and a higher volume of intake needed to attain satiation, while delayed gastric emptying time leads to a lower ingested volume requirement for satiation [63]. Paradoxically, individuals with PWS have delayed gastric emptying despite apparent impaired satiation [64, 65]. Gastric dilatation, predisposing to rupture, and gastroparesis have been observed in PWS, the latter suggestive of vagal nerve dysfunction [64].

A primary hypothalamic defect has been postulated to drive the hyperphagia in PWS, particularly since many of the appetite-regulatory pathways identified in rodents and humans have been localized to the arcuate nucleus of the hypothalamus. A current model of appetite regulation includes peptides generated within the gastrointestinal system or body tissues that are released into the bloodstream (endocrine) or nervous system (neurocrine). These peptides then feedback to specific receptors in the hypothalamus, resulting in generation of signaling within the central nervous system and back to the body tissues. Defects in this system could theoretically lead to hyperphagia, as may occur in rare forms of monogenic obesity. However, as of this writing, no relevant functional, structural, or genetic hypothalamic abnormalities have been identified in PWS.

The following list summarizes current knowledge of several postulated appetite-regulatory peptides in relation to PWS. Overall, although PWS may be associated with aberrations in the

levels of some of these peptides, a role for the any of these peptides in the pathogenesis of PWS has not been defined. However, this does not exclude the possibility of a therapeutic role for pharmacologic manipulation of one or more of these systems.

1. Cholecystokinin (CCK)

CCK is produced by the endocrine I cells in the duodenum and jejunum in response to dietary fat and amino acids and gastric acid. CCK delays gastric emptying, inhibits release of gastric acid, and stimulates pancreatic enzyme secretion, gallbladder contraction, intestinal motility, insulin secretion, and pancreatic polypeptide secretion. In the brain, CCK has been identified in the cerebral cortex and is postulated to be responsible for initiating satiety during a meal [66].

In PWS, serum levels of CCK are normal [67], but unlike in non-PWS controls, fasting CCK was not correlated with free fatty acid levels [68]. In response to a protein meal, CCK levels rise normally in individuals with PWS [69].

2. Pancreatic Polypeptides

Pancreatic polypeptide (PP), peptide YY (PYY), and neuropeptide Y (NPY) are produced in the pancreatic islets of Langerhans (PP), the large and small bowel (PYY), and peptidergic neurons of the stomach, small intestine, and central nervous system (NPY). PP secretion is primarily stimulated by protein intake and cholinergic activity. PYY secretion is stimulated by mixed meals and oleic acid. NPY functions as a neurotransmitter, with high concentrations in the arcuate nucleus of the hypothalamus. PP and PYY are postulated to play a role in satiety.

PP secretion in response to a protein meal has been reported to be deficient in PWS [69, 70]. Short-term infusion of PP was initially reported to cause a mild inhibition of food intake in females with PWS [71]; however, more detailed investigation indicated no effect [72].

The postprandial rise in circulating PYY levels has been reported to be low in non-PWS obese individuals, and PYY infusion was observed to cause a reduction in food intake [73]. Low fasting PYY levels have been reported in infants and children with PWS [74], although other studies have demonstrated normal fasting and elevated postprandial levels in children with PWS [75] and a blunted postprandial rise in adults with PWS [76]. Limited data indicate no differences in brain expression of PYY or its receptor were found in PWS vs. controls [77].

NPY activity in the hypothalamus is postulated to stimulate food intake. Hypothalamic NPY neurons were found to be normal in PWS [78]. Serum levels of NPY are reported to be low-normal in adults with PWS and do not change with GH therapy [79].

3. Orexins

Orexin A and B (*aka* hypocretins) are alternate proteolytic products of a precursor protein encoded by the hypocretin neuropeptide precursor gene (*HCRT*), a gene which is expressed in the hypothalamus. Orexins, particularly orexin A (*aka* hypocretin-1), have been implicated in regulation of sleep/wake cycles and energy expenditure, stimulation of feeding behavior, and other neurologic, behavior, and metabolic functions. Cerebrospinal fluid orexin A levels are reported to be low in individuals with PWS [80, 81], suggesting a relationship to narcolepsy-like symptoms; however, the number of orexin A containing neurons in the lateral hypothalamus is apparently not decreased, as has been observed in non-PWS narcolepsy. However, orexin expression was increased in lymphoblastoid cells from adults with PWS [82], and orexin A level was elevated in PWS relative to controls [83]. The potential role(s) of orexins in the pathophysiology in PWS remains undefined.

4. Agouti-Gene-Related Protein (AGRP)

AGRP production is co-localized with NPY in the hypothalamus. In animal studies, AGRP stimulates food intake by inhibiting the actions of melanocortin, an anorexigenic neurocrine peptide. AGRP expression was reported to be decreased in the neonatal mouse model of PWS,

in which there is failure to gain weight (as with human PWS) [84]. However, AGRP neurons appear to be normal in older individuals with PWS [78].

5. Ghrelin

Ghrelin is a peptide derived from preproghrelin that is secreted by the oxyntic glands of the gastric mucosa. Posttranslational activation occurs via acylation, usually by attachment of octanoic acid, a process medicated by the enzyme ghrelin O-acyltransferase. Circulating ghrelin levels rise progressively during fasting and decrease rapidly after a meal. Ghrelin crosses the blood-brain barrier and may interact with a variety of neuronal systems. Pharmacologic administration of ghrelin to mice results in increased food intake, an effect mediated by NPY/AGRP neurons [85]. However, the ghrelin knockout (deficient) mouse has no apparent defect in appetite or any other body function [86].

Serum ghrelin levels are elevated in PWS relative to obese and lean controls [74, 87–91]. Serum ghrelin levels decrease in response to meals and somatostatin administration in PWS [92], although a blunted postprandial response may occur in adults with PWS [76]. Elevated ghrelin has been associated with increased gastric motility in rodents; however, gastric emptying was delayed in PWS versus controls [65].

Un-acylated ghrelin may antagonize the effects of acylated (active) ghrelin, and relatively elevated un-acylated to acylated ghrelin has been reported in infants with PWS [93]. A 14-day randomized placebo-controlled trial of an un-acylated ghrelin analog in PWS showed a reduction in hyperphagia, as assessed by standardized questionnaire [94].

6. Obestatin

Obestatin is a peptide produced from C-ghrelin, which is in turn a product of preproghrelin, which is also the parent propeptide for ghrelin. As opposed to ghrelin, obestatin is postulated to suppress appetite. Elevated circulating obestatin levels have been reported in infants with PWS, with lesser or no significant elevation in older individuals [95, 96].

7. Endorphins

Endorphins are proteolytic products of β-lipotropin, a cleavage product of proopiomelanocortin (POMC). POMC is produced primarily by pituitary corticotrophs and is also the precursor for melanotropins and adrenocorticotropic hormone. β-lipotropin gives rise to β-endorphin, which in turn can be proteolyzed to α-endorphin and γ-endorphin. All three endorphins are present in humans and are produced in response to pain, blunting the pain signal by blocking the release of substance P from peripheral nerves. Unlike its cleavage products, β-endorphin binds to opiate receptors. Endorphins are also involved in certain pleasure responses, such as during eating of certain foods (e.g., chocolate) and during sexual activity. Endorphins have been postulated to play a role in various types of eating disorders, including PWS [97]. Serum levels of β-endorphin are reported to be normal [98] or elevated [98, 99] in children with PWS. Administration of the opioid inhibitor, naloxone, had no effect on food intake [100].

8. Leptin

Leptin is produced by white adipose tissue, and except in those conditions involving genetic defects in leptin or leptin receptor expression, serum leptin levels correlate directly with body fat. In PWS, leptin levels are increased and appear to be directly correlated with body fat [101–104]. No differences in adipose tissue leptin mRNA were found in PWS compared to non-syndromic obesity. Growth hormone therapy may decrease leptin levels in PWS; this effect is probably related to decreased fat mass [105–107].

9. Oxytocin

Oxytocin is a peptide hormone produced in the hypothalamus and released from the posterior pituitary gland primarily during childbirth and

lactation. An injectable pharmacologic preparation of oxytocin is commonly used to stimulate uterine contractions. Oxytocin may also have physiologic roles in bonding and social behavior and may suppress eating behavior. Significantly decreased oxytocin staining was observed in the hypothalamic paraventricular nuclei of individuals with PWS [37], while elevated oxytocin levels have been reported in cerebrospinal fluid [38] and in the peripheral circulation [108]. Several clinical trials involving intranasal administration of oxytocin have not demonstrated convincing evidence of a significant effect on social or eating behavior in individuals with PWS [109, 110].

The possibility exists that the primary disorder causing hyperphagia may involve a defect in peripheral satiety signaling, perhaps related to an abnormality in intermediary metabolism (nutrient shuttling) and/or gastric hypotonia. A peripheral defect would agree with the clinical observation that the eating behavior in PWS more closely resembles nutritional deprivation or starvation than accentuated normal hunger [111, 112].

Energy Expenditure

Previous studies have described alterations in metabolic rate in individuals with PWS. Schoeller et al. [113] noted problems with use of common mathematical formulae to predict the basal metabolic rate (BMR) in adults with PWS and advocated use of the Cunningham BMR formula to adjust for the deficit in lean mass (FFM). Subsequent studies have demonstrated a low basal metabolic rate with varied interpretation of data dependent upon the technique of body composition analysis [114, 115]. However, although resting energy expenditure may be normal or near normal for lean mass, lean mass is deficient, leading to deficient expenditure for total body mass [113, 116, 117].

Despite differences in body composition, energy expenditure during physical activity is similar to that of controls when corrected for lean mass [118–120]. However, individuals with PWS are less active than controls [115, 121]. The combination of diminished BMR and activity level necessitates lower caloric intake or a significant increase in physical activity to avoid excessive weight gain.

Associated Morbidities

Body fat itself can be a direct cause of morbidity or mortality. Fat embolism is an example of direct fat-related morbidity, but this condition is not reported to occur with increased frequency in PWS. In PWS, the increased *proportion* of fat to lean mass (regardless of weight) is largely the result of decreased muscle mass. The resultant hypotonia is a major contributor to morbidity and mortality, as discussed in previous sections. However, as body weight increases, the fat mass itself becomes problematic. Excess body fat can contribute indirectly to pathophysiology in two ways: (1) physical complications due to the fat mass and (2) metabolic disorders related to fat.

The detrimental effects of excess fat mass are well recognized. Increased fat is associated with respiratory impairment and obstructive sleep apnea in PWS and non-PWS populations. The sheer weight of excess fat in the presence of low muscle mass also contributes to impaired physical mobility and difficulty with daily tasks. Many adults with PWS adopt a typical hypotonic posturing, with both arms folded across the upper abdomen, and may develop difficulty with ambulation. Increased fat mass may also theoretically exacerbate scoliosis and fracture risk.

Metabolic effects of increased body fat have been well defined in the general non-PWS population. In children, obesity has been associated with accelerated height growth, advanced skeletal maturation, early adrenarche, and central precocious puberty.

In children with PWS, premature adrenarche occurs in a relatively small subset of cases [122–124], as manifested by early (e.g., before age 8 to 9 years old) appearance of pubic hair. Anecdotal experience suggests that the frequency of premature adrenarche is less than might be expected in a similarly obese non-PWS

population. In affected children, the increased linear growth rate due to adrenarche may resemble a normal, non-PWS growth pattern, although accelerated for PWS. Unfortunately, the result is often extreme adult short stature due to premature epiphyseal closure, which is quite different from the normal stature attained by non-PWS children with obesity-related premature adrenarche. Therefore, premature adrenarche is not a benign condition in PWS as it usually is in non-PWS obese children.

Obesity-related prediabetes and type 2 diabetes mellitus (T2DM) can occur in patients with PWS and are indistinguishable from these conditions in non-PWS obese individuals. However, individuals with PWS may have a lower risk for insulin resistance and T2DM than would be expected based on the degree of obesity [125]. Average fasting insulin levels are low in children and adults with PWS, and there is a relative lack of clinical signs consistent with insulin resistance [71, 106, 126–128], arguing against an increased frequency of insulin resistance. In non-PWS individuals, conditions related to insulin resistance, including T2DM, are related to increased intra-abdominal visceral fat, as distinguished from subcutaneous fat. Lipid deposition in muscle and other body tissues may also be contributory. However, in obese individuals with PWS, subcutaneous but not visceral fat has been found to be increased [129, 130]; the mechanisms for this occurrence have not been defined.

Monitoring for prediabetes and T2DM should be a routine element of care for all individuals with PWS, and may include periodic measurement. Some cases of T2DM may present with the classic symptoms of diabetes mellitus: polyuria, polydipsia, and unexpected weight loss; ketoacidosis, obtundation, and disordered consciousness may occur in the most severe cases [131]. However, most individuals with prediabetes or T2DM will be asymptomatic. A classic, but not universal, physical sign of insulin resistance is acanthosis nigricans: hyperpigmented, velvet-textured skin in the nuchal, axillary, inguinal, and other folds of the body thought to be due to direct or indirect effects of hyperinsulinemia on keratinocytes.

Treatment

Nutritional management of PWS can be separated into three major areas of concern:

1. Maintenance of adequate nutrition in infancy
2. Prevention of obesity and optimization of lean mass
3. Treatment of obesity and obesity-related morbidities

Evolving clinical needs for the individual with PWS require adaptation of nutritional support. During infancy, diminished muscle tone affects the volume of caloric intake during feedings. A variety of techniques are available for nutritional support of the infant with PWS including adaptive feeding bottles and nipples (e.g., Haberman feeder, cleft palate nurser, adaptive nipples), thickening agents (Thick-It, cereal), formula concentration, and nasogastric tubes. The feeding therapy utilized is determined by the adequacy of swallowing skills and nutritional status.

Nasogastric and gastrostomy feedings are commonly used to meet the nutritional needs of infants with PWS. Since gastrointestinal absorption and motility are essentially normal, intravenous total parenteral nutrition is usually not required. In infants receiving feedings primarily through a non-oral route, oral feedings as tolerated and nonnutritive sucking should be continued to encourage development of oromotor strength and coordination.

Intake parameters during infancy can be patterned along standardized guidelines [132]. During the first 6 months of life, breast milk and infant formula should serve as the primary nutritional source and should be given in usual amounts. Solids are generally introduced at 5 to 6 months of age and advanced in texture, dependent upon oral motor skills. Higher-calorie solids, desserts, and juices are commonly avoided. Through clinical examination and close monitoring of growth data, dietary intake can be appropriately adjusted to maintain adequate nutrition while avoiding excessive weight gain.

Nutritional strategies beyond the toddler years focus on avoidance of obesity. Limited studies

[133, 134] have evaluated the caloric requirements for individuals with PWS who were not treated with growth hormone [133, 134]. For children with PWS, weight maintenance has been reported with intakes of 8 to 11 kcal/cm/day (non-PWS children require 11–14 kcal/cm/day; cm = height); weight loss has been documented with intakes of 7 kcal/cm/day. However, these guidelines may be excessive for children who are unusually inactive and, conversely, inadequate for children with PWS receiving growth hormone therapy.

For adolescents and adults with PWS, a general recommendation has been 800 to 1000 kcal/day for weight loss, which is a significant reduction from usual food intake in the general population. Therefore, an individual PWS who follows this recommendation would probably need to have different food preparation and provision from the rest of the household.

A typical approach to a calorie-restricted weight control treatment plan is to introduce a balanced calorie reduction, with maintenance of standardized carbohydrate-protein-fat proportions (i.e., 60%, 15%, 25%, respectively). Emphasis on low-glycemic-index carbohydrates (e.g., slowly digested complex carbohydrates rather than high-sugar foods) may also reduce insulin secretion, facilitate optimal nutrient utilization, and have a positive effect on satiety, although these effects have not been studied in individuals with PWS.

Adherence to a calorie-restricted diet requires intensive and continuous monitoring of intake and regular dietary counseling, including analysis of food histories and attention to possible associated nutrient deficiencies. Behavioral aspects of this plan require attention to all potential sources for intake including cafeterias, school buses, classroom activities, vending machine access, neighbors, and convenience stores as well as home access (e.g., pantry, garbage cans, refrigerator, tabletop). Locks on kitchen doors and refrigerators are often recommended elements of this plan.

There is no doubt that total calorie restriction will achieve weight maintenance or loss if completely implemented; however, it remains unresolved as to whether this approach is justified in view of the physiology. As mentioned in a previous section, the food foraging and apparently insatiable appetite in PWS may be triggered by internal mechanisms that more closely resemble true starvation than non-PWS pre-meal hunger or eating behavior. If this is true, then the intentional restriction of all intake could have detrimental effects on overall behavior and well-being and may, in fact, augment foraging and food-sneaking behavior.

An equally important issue relates to adverse effects on body composition. Although increased body fat and overweight is a major visible morbidity in PWS, a more crucial functional morbidity is the lack of lean mass. In non-PWS individuals, induction of an energy deficit (e.g., fasting, total calorie restriction) and weight loss using a balanced nutrient intake results in loss of not only fat mass but also lean mass. In non-PWS individuals, excess body fat will provide a relative protection against loss of lean mass (i.e., thinner individuals lose proportionately more lean mass than obese individuals during weight loss) [135].

As stated by Dr. Gilbert Forbes, a pioneer in this field of research, “There is no level of reduced energy intake that will completely spare LBM [lean body mass] when significant amounts of body weight are lost” [54]. In individuals with PWS, where total lean mass is deficient even in the presence of obesity, a balanced calorie restriction diet can be expected to have a detrimental effect on lean mass.

However, lean mass can be at least relatively preserved during calorie deficit by preferentially conserving protein intake. The initial observations of this phenomenon preceded the currently popular low-carbohydrate, increased protein diets [54]. In a short-term metabolic unit study in four patients with PWS, a protein-sparing (1.5 gm of meat protein per kg body weight), ketogenic, modified fast preserved positive nitrogen balance and lean body mass in the presence of significant weight reduction [136]. A similar nutritional approach in an obese ventilator-dependent adolescent with PWS apparently facilitated weight management and weaning from the ventilator [137].

In addition to potential effects on preservation of lean mass, protein may have a greater positive effect on satiety than carbohydrates or fat, as demonstrated in both short- and long-term human studies [138–140]. Although this effect has not yet been fully investigated in individuals with PWS [141], it was postulated to occur in outpatient follow-up of patients involved in the previously mentioned study using a protein-sparing fast [136] and was demonstrated in randomized crossover studies comparing high-protein to standard meals in children with PWS [142].

A ketogenic protein-sparing diet may have limited feasibility for most individuals with PWS, especially as a long-term treatment [143]. However, several other approaches to high-protein, lower-carbohydrate meal planning are available. Popular diets using this approach typically result in 28% to 35% calories from protein, 8% to 40% from carbohydrate, and the remainder from fat [138]. One of the authors (PDKL) has prescribed modified lower-carbohydrate, lower-fat guidelines in his PWS clinics for several years, an approach which is similar to other, perhaps more stringent, regimens [144, 145]. The basic five-step approach is as follows: (1) elimination of added sugar and foods containing >5 grams of sugar per serving; (2) limitation of complex carbohydrates to one to two servings three times daily, with one serving = 15 gm of carbohydrate; (3) avoidance of fried and fatty foods; (4) encouragement of lean protein intake; and (5) provision of "free foods" – that is, carb-free, low-fat, low-calorie – for ad lib snacking and/or foraging. In addition, an exercise guideline of 30 minutes sustained activity, three to five times weekly, is recommended. This regimen is provided as a one-page guideline and reviewed in detail during clinic visits. Individuals who adhere to this simple plan experience a substantial reduction in total calories and maintenance of healthy weight. This approach has the advantages of being easy to learn (requires teaching of food label readings and basic carbohydrate counting), relatively straightforward implementation, and possible integration into usual household eating patterns. More structured dietary regimens can be added to this basic program for individual patients.

Whatever dietary approach to weight control is taken, it is important that it be logical, consistent, easily implemented, emphasized at each clinic visit, and carefully monitored. Modifications should be made for individual patients, and in children developmental changes should be taken into account.

Pharmacotherapy

Pharmacologic agents for weight management should be considered as adjuncts and not primary treatment modalities. None of the appetite suppressant or anti-absorptive agents marketed for obesity treatment have shown efficacy in PWS, and systematic studies have not been published. Some of the psychotropic agents commonly used in PWS have been anecdotally reported to control food foraging behavior, but exacerbation of overeating has also been observed [146]. Growth hormone therapy may have a beneficial effect on eating behavior and development of obesity particularly if initiated in infancy. In a short-term uncontrolled trial, the anti-epileptic medication, topiramate, was reported to improve eating and other behaviors in seven patients with PWS, resulting in weight loss in three [147]; however, several of the subjects were on concomitant medications, and the overall results were not entirely conclusive.

Published reports [148, 149] indicate that metformin may have efficacy for treatment of obesity in PWS. Personal experience (PDKL) suggests that metformin efficacy is increased when coupled with a carbohydrate controlled dietary regimen, as described above. Similar results have been reported in treatment of non-PWS obesity [144, 145, 150, 151].

As of this writing, a few other candidate treatments for hyperphagia and obesity in individuals with PWS have been studied or are in development. As described in a previous section, intranasal oxytocin has been the subject of several clinical trials; overall results are inconclusive.

However, positive effects on hyperphagia were reported for a phase 2 study of intranasal carbetocin [152], an oxytocin analog currently used for treatment of postpartum hemorrhage. A phase 3 study was completed in May 2020, and results have not been published as of this writing. However, top-line results released by the manufacturer in August 2020 indicated that the primary study endpoint was not met.

A 6-month open-label, non-randomized, uncontrolled study of exenatide treatment showed significant decreases in appetite scores and hemoglobin A1c levels, but no changes in weight, measures of adiposity, or ghrelin levels [153].

A phase 2 study of setmelanotide, a melanocortin-4 receptor agonist, on weight and hyperphagia in individuals with PWS was completed in 2016 and reportedly showed a modest effect on reduction of hyperphagia and no effect on weight. As of this writing, study data have not been published. The same sponsor has recently announced plans to study the effectiveness of a ghrelin O-acyltransferase inhibitor in PWS.

A 26-week, phase 3, randomized, controlled trial of beloranib, a methionine aminopeptidase inhibitor 2, in PWS was prematurely terminated due to an imbalance in venous thrombotic events, including two fatal cases of pulmonary embolism. Intention-to-treat analysis showed statistical benefits for hyperphagia and weight; however, further studies are not planned as of this writing [154].

A 10-week, phase 2, open-label trial of diazoxide choline in adolescents and adults with PWS showed beneficial effects on measures of hyperphagia, reduction of body fat, and increased lean mass [155]. The study design included a 4-week randomized, double-blind, placebo-controlled period at the end of the 10-week open-label period; however, results from this period have not been published.

An uncontrolled, proof-of-concept study of 12 adolescents and adults with PWS showed beneficial effects of transcranial direct current stimulation, a noninvasive procedure involving electrical stimulation of specific brain areas, on hyperphagia and behavior [156].

Bariatric Surgery

Surgical options for weight management are not generally recommended in PWS. Bariatric surgery causes weight loss through either a diminished capacity for food intake and/or via reduced digestion and absorption of food. In non-PWS obesity, studies in adolescents and adults show efficacy in promoting weight loss, although surgical risks, gastrointestinal problems, and malabsorption are concerns.

Experience with bariatric surgery in PWS is summarized in Table 6.1.

No significant or lasting effect of bariatric surgery on hyperphagia in PWS has been demonstrated. Therefore, the need for dietary intervention and monitoring is not eliminated. Over the long term, weight gain may recur after the patient develops compensatory dietary strategies. At the current time, bariatric surgery should be considered only in severe cases in which serious obesity-related morbidities are present and rapid weight loss is expected to be beneficial [173].

Special Nutritional Considerations

Vitamin and mineral supplementation is highly recommended for individuals with PWS and particularly for those on a balanced calorie restriction diet. Hypocaloric balanced calorie reduction diets can be deficient in calcium, iron, vitamin D, vitamin E, biotin, pantothenic acid, magnesium, zinc, and copper; multivitamin and mineral supplementation is recommended in the publication. In addition, many individuals with PWS have limited sun exposure, especially those affected with hypopigmentation. Since a large proportion of the body stores of vitamin D are synthesized in response to sunlight, lack of sun exposure can result in vitamin D deficiency and an increased risk for osteoporosis.

As a rule, it is recommended that all patients with PWS receive daily multivitamin and mineral supplementation in consideration of their individualized meal plan and sun exposure. An over-the-counter preparation may be adequate for

Table 6.1 Bariatric surgery in Prader-Willi syndrome

Publication year	Procedure	*N*	Age(s) or average age (years)*	Weight (kg)*	Results	Complications
1975, 1980 [157, 158]	91% gastric bypass 9% gastroplasty	11	13	85	Weight 74 kg at 1 year, 85 kg at 5 years post procedure	54% required revision due to inadequate weight loss Weight regain 1 wound infection 1 dumping/diarrhea 1 death from uncontrolled weight gain
1981 [159]	Vagotomy	1	17	120	29 kg weight loss followed by 20 kg weight regain	Weight regain
1983 [160]	Jejunoileal bypass	1	24	181	62 kg weight loss at year post procedure	Wound infection, thrombosis, pulmonary embolus, diarrhea
1991 [161]	Biliopancreatic diversion	3	27.6	84.5	Significant weight loss at 1 year, then regain at 2.5 to 6 years post procedure	Weight regain Diarrhea Deficiencies: vitamin D, vitamin B12, folate, iron
1992 [162]	Gastroplasty, vertical banded	1	21	57.4	Improved diabetes control to 24 months post procedure	Short-term weight loss, break in stable line followed by weight regain. Return to baseline diabetes control at 5 years post procedure
1997 [163]	Laparoscopic adjustable band	1	Not reported			Fatal postoperative bleeding
2000 [164]	Biliopancreatic diversion	1	24	80	26 kg weight loss followed by 21 kg weight gain	Weight regain
2001 [165]	Biliopancreatic diversion	15	21	127	56% weight loss at 3 years post procedure, followed by weight regain	Weight regain Two deaths from unrelated causes
2003 [166]	95% gastrectomy with Roux-en-Y gastric bypass	1	15	BMI 57.7 kg/m^2	BMI 30 kg/m^2 at 1 year post procedure	None reported
2003 [167]	Roux-en-Y gastric bypass	1	30	146	54 kg weight loss at 18 months post procedure, improved lipid profile	None reported
2014 [168]	Omega-loop gastric bypass	3	15, 18, 14	BMI 46.6, 41.6, 54.8 kg/m^2	BMI 32.0, 38.6, 36.6 kg/m^2 at 12, 6, and 24 months post procedure, respectively. Improved comorbidities	None reported

Table 6.1 (continued)

Publication year	Procedure	*N*	Age(s) or average age (years)*	Weight (kg)*	Results	Complications
2016 [169]	Laparoscopic sleeve gastrectomy	24	10.7	BMI 46.2 kg/m^2	Annual BMI decreased 14.7, 15.0, 12.2, 12.7, and 10.7 kg/m^2 from baseline 1 to 5 years post procedure, respectively. Improvement in obesity-related morbidities	No operative complications One case with recurrent OSA and heart failure 5 years post procedure
2018 [170]	Biliopancreatic diversion	1	25	BMI 55 kg/m^2	BMI reduced to 38.5 kg/m^2 1 year post procedure. Improved glucose and lipid levels	None reported
2019	Sleeve gastrectomy	1	16	223, BMI 80.9 kg/m^2	178 kg (BMI 64.59 kg/m^2) 6 months post procedure	No operative complications Recurrent hyperphagia at 6 months post procedure
2020 [171]	Anastomosis gastric bypass	2	16, 15	131.5 and 144 kg	106 kg at 17 months and 122.7 kg at 7 months post procedure. Improvement in morbidities	None reported
2020 [172]	Sleeve gastrectomy ($N = 2$), anastomosis gastric bypass (N-1), Roux-en-Y gastric bypass ($N = 1$)	5	19.2	BMI 47.9 ± 6.9	Initial weight loss not maintained at 10 years post procedure. No improvement in comorbidities	Weight regain

many patients. Others may require additional monitored supplementation with calcium, trace minerals, and vitamins. Trace mineral, iron, and fat-soluble vitamin supplementation should be carefully monitored to avoid overload.

Obesity-Related Morbidities

Premature Adrenarche

In children without PWS, premature adrenarche is usually a benign condition that does not require specific therapy; indeed, specific therapies have not been proven to have efficacy [174]. In some cases, premature adrenarche may be associated with early central puberty, which may require treatment. As mentioned previously, premature adrenarche in children with PWS is not a benign condition since it is associated with severe short stature and an inadequate increase in height velocity [123, 124]. Although obesity is thought to be pathogenetic for this condition, there is no evidence that intensive weight control after onset will slow the progress of the adrenarche. Prevention of predisposing factors for premature adrenarche via weight management beginning in very early childhood is the best recommendation at this point. In cases where the process has already started, growth hormone therapy should be considered even if current height is normal to optimize final adult height.

Type 2 Diabetes Mellitus

The treatment of T2DM in PWS should follow current standard-of-care guidelines for these conditions in the non-PWS population. A comprehensive discussion of this topic is beyond the scope of this chapter.

In general, the first-line approach should include diet and exercise, as described above for treatment of obesity and overweight; in milder

cases, these therapies may lead to complete resolution of the condition. Metformin should be considered a first-line pharmacotherapy [148, 149, 175]. Insulin may be necessary in cases where there is evidence of insulin deficiency (i.e., ketoacidosis) but should be avoided in all other cases since it may hinder treatment of obesity. Other antidiabetic agents can be used if the above treatment plan does not achieve the desired goal, which in most cases should be normalization of hemoglobin A1c levels, or at least a lowering of the level to <7.5%.

There have been surprisingly few reports of diabetes-related complications [176, 177] or early cardiovascular events in individuals with PWS and T2DM. However, individuals with diabetes mellitus should be routinely monitored for evidence of retinopathy, nephropathy, hypertension, and cardiovascular disease, with appropriate therapy as needed as per general standard-of-care practice guidelines.

Other Obesity-Related Conditions

Nonalcoholic fatty liver disease is a major cause of liver failure in the general population, with incidence and prevalence directly related to obesity. Individuals with PWS may have a lower risk for developing this condition as compared to controls [49, 178]. However, routine monitoring of transaminase levels and, if indicated, liver imaging should be considered. Dietary modification and metformin are current treatment modalities.

Similarly, obesity-related dyslipidemia and hypertriglyceridemia are prevalent in the general population. Data for PWS are limited and indicate a lower-than-expected occurrence; however, periodic screening and treatment can be recommended, particularly if there is a positive family history.

Obesity has been associated with an increased risk for cancer in the general population. However, a similar occurrence has not been demonstrated for PWS.

Breathing problems, respiratory compromise, and orthopedic (bone and joint) disorders all occur with higher frequency in obese individuals and are discussed in other chapters of this book.

Measurement of Body Composition

The measurement and monitoring of body composition is an essential element in clinical research and management of individuals with PWS. Body composition measurements may be used to diagnose decreased bone mineral density (osteopenia, osteoporosis) and monitor changes in total body fat and nonfat mass.

Anthropometry

Anthropometry refers to body measurements, such as length or height, weight, circumferences, and skinfold thickness.

Height growth is an essential feature of human development and should be measured for all children at regular intervals. The measurements should be plotted to the nearest fractional age on charts compiled from the background reference population. Standardized height growth charts have been generated for an international population by the World Health Organization (WHO, www.who.int) and are also available for national populations, for example, for the US population (U.S. Centers for Disease Control, www.cdc.gov). Children under 2 years of age should be measured using recumbent length. Height velocity charts are also available. Detailed procedures for accurate measurement and calculation of height and height velocity are available, for example, on the CDC website.

Height growth is a measure of long bone (primarily leg and spine) growth, which in turn is dependent on a number of genetic, hormonal, structural, and mechanical factors. Abnormal height growth in children can be the first sign of a systemic abnormality. As mentioned previously, height growth in children with PWS is highly variable but usually abnormally low relative to the non-PWS reference population starting at or before 3 years old. The average final adult height in PWS is approximately 2 standard devia-

tions below the mean for the reference population (Appendix C) [179–181]. Scoliosis, if present, may also account for loss of height growth.

Weight is a measure of total body mass, *regardless of composition*. As a standalone measurement, it has little intrinsic utility, even if compared to reference population data. The clinical value of a weight measurement can improve when analyzed in conjunction with height, for example, as weight-for-height or calculated body mass index. Assuming that fat and lean mass are present in a predictable proportion (see previous discussion regarding the "companionship rule" above), proportionality of weight to height can provide an index of body fatness. However, in conditions where there is an excess proportion of lean mass (e.g., body building) or deficient lean mass with excess fat mass (e.g., PWS), these ratios fail to provide an accurate estimate of body fat.

Anthropometric measurements for head circumference, hand and foot length, and other body parts are available for non-PWS reference populations and for PWS (see Appendix C). Head circumference measurements are primarily used as an indicator of brain growth in infants and toddlers under 3 years of age. Careful monitoring of head growth is also important for detection of craniosynostosis or premature closure of the cranial sutures, which can result in severe neurologic sequelae. One such case in PWS has been published [182], and the authors are aware of other cases.

Waist circumference and waist-to-hip circumference ratios have been used to estimate visceral fat and consequent risks for T2DM and cardiovascular disease in non-PWS adults. However, this correlation is likely to be less reliable in PWS since visceral fat may not be increased despite an overall increase in fat mass [129].

Skinfold thicknesses, measured using calipers at selected body sites, have been used to estimate body fat and nonfat mass. Skinfold thickness is primarily a measure of subcutaneous fat. Using assumptions and validated algorithms regarding the proportions of subcutaneous fat to other body compartments, fat and lean mass can be estimated. Although skinfold thickness measurements have been used in several key studies of PWS [58, 183, 184], inter-observer variability and lack of validated disease-specific standards and algorithms are major limitations to routine clinical use [185].

Although anthropometry has been used for many decades to indirectly estimate body composition, these techniques are less commonly used for that purpose today. If detailed body composition analysis is needed, more sophisticated techniques are used, as discussed below.

Body Composition Modeling

The first step in accurately determining body composition is to select a model that provides clinically relevant measurements (Fig. 6.3).

The most extreme form of body composition analysis, elemental or chemical analysis after ashing, is primarily of research interest since it cannot be feasibly applied to an individual living organism. Elemental analysis can be performed in vivo using isotope counting and neutron activation methods [186]; however, these measurements currently have limited availability and clinical utility and will not be discussed.

The simplest clinically useful model of body composition, the two-compartment (2-C) model, divides total body mass or weight (Wt) into fat mass (FM) and fat-free mass (FFM). Body fatness, in turn, can be defined as the FM/Wt ratio, expressed as a percentage. The basic 2-C model requires only one measurement to be made and is the easiest to use when the assessment of body fat mass or fatness is the primary aim.

More detailed clinical models [187, 188, 194, 195] particularly for considering issues related to nutrition or growth, separate the FFM into components, creating a multicompartment model (Fig. 6.3). For example, FFM can be separated into bone mineral and non-bone lean tissue for a three-compartment model, or water, protein (muscle), and mineral (bone) for a four-compartment (4-C) model. Direct assay of FFM components has been facilitated by imaging techniques such as dual-energy X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI).

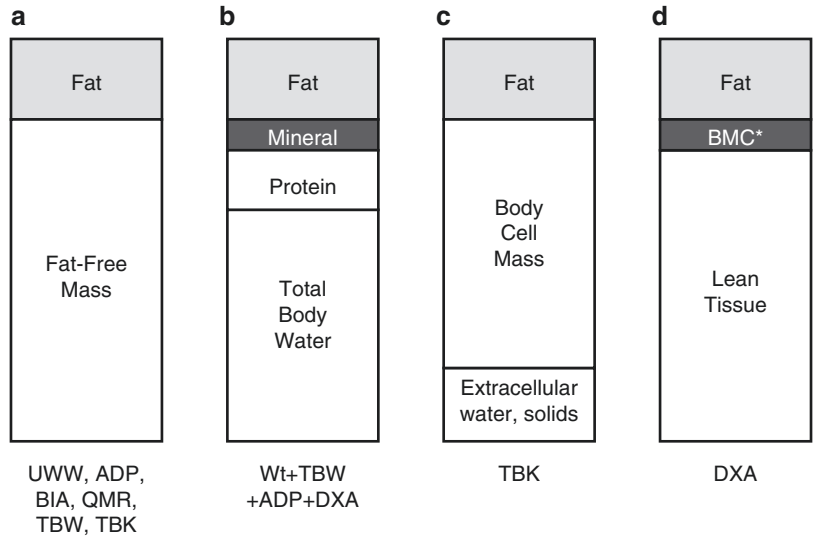

Fig. 6.3 Multicompartment models of body composition and related measurement methods. (**a**) Basic two-compartment model: weight = fat + fat-free mass (FFM). Measured by several different methods. (**b**) Classic four-compartment model: mineral, protein, and water subcompartments of FFM. Measured using a combination of methods. (**c**) Body cell mass and extracellular water and solid subcompartments of FFM. (**d**) Three-compartment model used by the dual-energy X-ray absorptiometry (DXA) model. *BMC: bone mineral content

In the following sections of this chapter, the various methods that are available will be described in the context of their application in two-, three-, and four-compartment models of body composition.

Methods Based on the Two-Compartment (2-C) Model

A usual 2-C model separates total mass into FM and FFM. For short-term longitudinal studies in healthy subjects, using age- and gender-adjusted constants, the 2-C model is adequate for the assessment of changes in body fatness. However, it does not provide information about components of the FFM.

Underwater weighing For this method, the model assumptions are that Wt = FM + FFM and that total body volume = FM + FFM volumes ($Vol_{TB} = Vol_{FM} + Vol_{FFM}$). An accurate measurement of Wt is relatively easy to achieve, that is, using a weight scale. However, the measurement of body volume is more challenging.

The classic technique of measuring body volume, underwater weighing (UWW, or hydrostatic weighing), relies on Archimedes' principle, which states that a body immersed in a fluid is buoyed up by a force equal to the weight of the displaced fluid. The UWW procedure involves measuring body weight while totally submerged underwater, after exhalation of air from the lungs, wearing a tight-fitting bathing suit and cap to cover scalp hair. The body volume is calculated by subtracting the underwater weight from the regularly measured body weight. The weight differential, which is equal to the weight of displaced water, is then divided by the density of water. This number is then adjusted for the measured residual lung volume.

The density of the body (ρ_{TB}) is the ratio of body weight (Wt) to body volume (Vol_{TB}). The classic UWW relationship between body fatness (%FM) and body density (ρ_{TB}) for a two-compartment model is $\%FM = 100 \times [(k_1/\rho_{TB}) + k_2]$, where the constants ($k_1$, k_2) are determined by the values selected for the densities of the fat and fat-free mass (ρ_{FM} and ρ_{FFM}) [24, 173]. The density of fat can be assumed to be constant

(0. 9004 g/cc), whereas the density of FFM is not constant, changes with growth [189], and is altered by diseases and medications. Since body water is the major contributor to the mass and volume of the FFM, changes in the relative water content (hydration) will have significant effects on ρ_{FFM}. Other components of the FFM can also change, but these have a secondary impact compared with hydration.

Air displacement plethysmography There can be several reasons why the underwater weighing technique cannot be used, for example, lack of necessary equipment, fear of water, difficulty breathing underwater, and too buoyant to be easily submerged for underwater weighing. An alternative technique called air displacement plethysmography (ADP) can also be used to measure body volume. The advantage of ADP is that the problems related to water are eliminated although the subject still needs to wear a tight-fitting bathing suit and cap to cover scalp hair. The objective is to determine the volume of air that is displaced by the subject's body [189, 190]. At present, there are two commercial ADP instruments available in the United States: BOD POD for adults and children and PEA POD for infants (COSMED USA Inc., Concord, CA).

The ADP technique is based on Boyle's law for gases: pressure multiplied by volume is constant if temperature does not change. Poisson's law for gases is also used to adjust for breathing (heated moist air coming from the lungs) and for the isothermal effects of air in contact with the skin and body hair.

For the BOD POD measurement, the subject sits on a bench in a small chamber which is connected via a diaphragm to a reference chamber behind the bench. A smaller seating option is available for children between 2 years old and 6 years old. The door (which has a large window) is closed, the diaphragm is oscillated at a low frequency, and the pressure difference between the two chambers is measured. The BOD POD instrument has a built-in spirometer system that can be used to measure the subject's residual lung volume. It should be noted that without preliminary training, the spirometer procedure can be difficult for some subjects to perform correctly.

The PEA POD uses similar technology with a much smaller "patient tray."

ADP estimates of body volume are highly correlated with those for UWW, and the two results are virtually interchangeable for healthy adults [190]. Additional studies with very young children may be needed, especially where body composition may be abnormal. However, it is reasonable to state that the ADP technology has largely replaced the underwater weighing technique for 2-C analysis in adult and pediatric populations.

Total body water and potassium Two alternate methods can be used in a 2-C model to estimate body fatness by measuring body water or cellular components of the FFM. The body composition parameters that are measured for these methods are total body water (TBW) and total body potassium (TBK), respectively [186]. For these two assays, the respective 2-C equations for body fatness are as follows:

$$\%\mathrm{FM}_{\mathrm{TBW}} = 100 \times \left(\mathrm{Wt} - \mathrm{TBW} / k_3\right) / \mathrm{Wt}$$
$$\%\mathrm{FM}_{\mathrm{TBK}} = 100 \times \left(\mathrm{Wt} - \mathrm{TBK} / k_4\right) / \mathrm{Wt}$$

where the values for k_3 and k_4 are assumed to be relatively constant at a given age for a healthy subject. However, during infancy and childhood, the relative hydration and potassium content of the total FFM are not constant, and they may also be altered by disease and/or medications. Therefore, the same limitations that were present for the 2-C UWW or ADP models are also present for the 2-C TBW and TBK models. *This is an inherent limitation of the 2-C model and not the methods*. An advantage of the TBW and TBK assays, compared with UWW or ADP, is that these assays provide useful information about the composition of FFM.

For the TBW assay, a dilution technique is utilized. The subject drinks a small amount of isotope-labeled (nonradioactive) water. Several hours later, a body fluid sample (blood, urine, or saliva) is collected and stored for later analysis

using isotope-ratio mass spectroscopy (MS) or Fourier-transformed infrared spectroscopy (FT-IRS). Since the amount of the isotope given to the subject is known, and its concentration in the water part of the fluid sample is measured, the total volume of the dilution space can be easily calculated [191]. The value for the conversion constant (k_3) that is used most often is 0.732 for older children and adults, gradually increasing to 0.83 for infants. That is, FFM contains, on average, about 73.2% water for healthy children and adolescents. This percentage, however, may be altered with diseases, such as severe malnutrition or edema, and by some drugs. A clear advantage of the TBW technique is that bulky instrumentation is not needed for isotope administration and sample collection, thus making it a suitable choice for field studies. The MS or FT-IRS analysis could be performed immediately, but the usual practice is to collect multiple samples for batched analysis at a later time.

The results of the TBK assay, on the other hand, can be obtained immediately. This assay takes advantage of a natural signal that is being constantly emitted from the potassium in the human body, which is primarily a component of the nonfat cell mass. A small fraction of natural potassium is radioactive (^{40}K), emitting characteristic gamma rays (1.46 MeV) at a rate of approximately 200 gammas per minute per gram of potassium. This signal can be detected external to the body using a whole-body counter [192]. Based on numerous studies over the past 40 years, the values for the conversion constant (k_4) are estimated at 59 to 61 mEq/kg for adult females and 62 to 64 mEq/kg for adult males. For infants, the ratio is reduced to approximately 43 mEq/kg because of increased hydration [186]. A major limitation with this assay is that the measurement instruments are not portable, and the number of available instruments and facilities is very limited. In addition, the typical TBK procedure requires 15 to 30 minutes, a significantly longer time period than most other assays. However, it is well recognized that the TBK assay is the best choice for monitoring body cell mass (BCM), the active metabolizing tissues of the FFM [192, 193]. In many diseases, knowledge of the patient's BCM status has a higher priority than knowledge of body fatness.

Bioelectrical impedance The bioelectrical techniques for assaying body composition were developed as alternatives to the TBW assay described above. The principle of the bioelectrical impedance technique is that the body has general electrical properties, which primarily reflect the volume of the FFM and its electrolyte content [194]. The attractiveness of bioelectrical impedance technology is that the instruments are relatively small and inexpensive, do not require extensive operator training, and produce immediate results. Two approaches have been developed for human use: single-frequency (50 kHz) bioelectrical impedance analysis (BIA) and multifrequency (5–1000 kHz) bioelectrical impedance spectroscopy (BIS).

For these procedures, electrodes are attached or placed in contact with selected body parts. As weak electrical current is passed between the electrodes, resistance (R) and reactance (Xc) are measured. The BIA assay uses a single frequency (50 kHz), while the BIS technique varies the frequency (5–1000 kHz). The basic BIA and BIS theory assumes that the Ht^2/R ratio is directly proportional to TBW or FFM [195]. Some BIA instruments have been designed to measure only the upper body (electrodes placed on the hands) or lower body (subject stands on the electrodes), while other methods have relied on segmental BIA measurements with multiple electrodes at several body sites.

There are at least 30 single-frequency BIA devices commercially available. Unfortunately, there are almost an equal number of algorithms to choose from for the calculation of TBW, FFM, or %FM. Furthermore, some investigators have suggested that disease-specific calibrations of BIA should be used [196]. Although this approach may, at first, appear attractive, this type of "workaround" simply avoids the more difficult issues related to the limited accuracy of the basic BIA theory and algorithms. In addition, there are challenges specific to pediatrics associated with bioelectrical impedance measurements that limit the accuracy of the technique [197].

A potential use of the data obtained by BIA devices is analysis of the phase angle (PhA) [198, 199]. PhA is associated with cell membrane integrity and the resistive behavior of tissues, which is dependent on tissue hydration [198]. The PhA, which is easily calculated using the R and Xc values from the BIA data, has been related to general health, physical fitness indicators such as percent body fat, and the status and prognosis of diseases such as cancer. PhA may be an index of health status rather than a direct measure of a body compartment, for example, fat or lean mass, and is currently best regarded as a research tool rather than a clinical measure.

Quantitative magnetic resonance Quantitative magnetic resonance (QMR) involves measuring the nuclear magnetic resonance signal within tissues, a signal that corresponds to the amount of hydrogen present [200]. Hydrogen nuclei within a magnetic field are exposed to various radio frequency pulses. The subsequent electromagnetic signals produced are characteristic of the tissues they represent. Processing these signals produces estimates of the mass of total body fat, lean, and free water. The measurement procedure itself is relatively efficient (1–3 minutes). Subjects are positioned prone within a measurement chamber. Slight movements are allowable, although the subjects are generally advised to keep still. The method has been applied successfully to animal models (e.g., mouse, piglet) [201, 202], and investigators have proceeded to test the validity of the method in humans [203, 204].

QMR has been shown to be perhaps the most precise of all the various body composition methods and has certainly been proven effective in animal studies. However, recent comparisons of body composition techniques have determined that PEAPOD and DXA (discussed below) had the highest accuracy for individual and group results, respectively, while QMR underestimated FM in infants and children [205].

As of this writing, commercially available QMR instruments are only available from Echo Medical Systems (Houston, TX). There are three different instrument designs, each tailored to measure a specific range of subjects according to size/age (infant, adolescent, adult), which could complicate longitudinal assessment across age groups. Nevertheless, the precision of the technique may still cause investigators to consider its use for body composition assessment.

Methods Based on the 3-Compartment (3-C) Model

Body density ± TBW A major limitation for the 2-C models based on body density (ρTB), that is, the UWW and ADP assays, is the assumption that TBW is a fixed percentage of the total FFM. This constraint can be overcome by using a three-compartment (3-C) model where a direct measurement of TBW is included. In this case, the %FM equation becomes:

$$\%\mathrm{FM} = 100 \times \left(2.118 / \rho_{TB}\right) - 0.78\,\mathrm{TBW}\right) / \left(\mathrm{Wt} - 1.354\right)$$

where the density of body fat and solids are 0. 9004 g/cc and 1.565 g/cc, respectively. The advantage of this model is that the hydration state of the FFM can be variable, without introducing additional error in the estimate for body fatness. The disadvantage of this approach is that two assays are needed, either UWW or ADP to determine body density and a separate TBW assay, which increases the complexity and decreases feasibility of the procedure.

Dual-energy X-ray absorptiometry Absorptiometric techniques were developed in the 1960s to examine bone status, primary due to concerns that astronauts would experience significant bone loss during space flight. Over the last few decades, significant advances have been made with this technology, evolving into the technique called dual-energy X- ray absorptiometry (DXA) [186], with DXA assays of the hip and spine as clinical standards for the assessment of bone

mineral density and fracture risk, especially in postmenopausal women.

During a DXA procedure, the subject lies supine on the exam table, clothed but with removal of any metal objects. An X-ray scanning arm passes over the targeted area of the body. The X-rays are attenuated during passage through body tissues; bone attenuates the X-rays to a greater degree than does soft tissue. The net signal is detected, analyzed for degree of attenuation, converted into pixels, and displayed as an image. For diagnosis and monitoring of osteoporosis, the scan is usually limited to the hip and/or vertebral lumbar spine, sites that are prone to osteoporotic fragility fractures. Whole-body DXA has been used for analysis of body composition, as described below. The DXA methodology is efficient and relatively noninvasive, a whole-body DXA scan can be obtained in approximately 3 minutes with a very low total radiation dose (<10 mSv).

For the clinical use of DXA as a quantitative measure of bone mineral density, the density and distribution of the overlying soft tissue must be known. This is accomplished by analyzing non-bone pixels in the image that are adjacent to bone-containing pixels for their relative fat-to-lean content and applying these results to bone-containing pixels. This analysis is the basis for extension of the DXA methodology to a quasi-three-compartment (3-C) body composition assay: bone mineral content (BMC), lean tissue mass (LTM), and FM. The sum of the bone-containing pixels provides a measurement called the bone area (BA); areal bone mineral density (BMD) is defined as BMC/BA. It should be noted that the DXA-derived BMD (g/cm^2) value is not true bone density (g/cm^3) but a projection of the total body mass onto a two-dimensional flat plane image of the body.

A clear advantage of whole-body DXA is that the body scan image can be divided into 10 general regions (head, arms, legs, trunk, pelvic, spine, etc.) with BMC, BMD, fat, and LTM calculated for each region. Thus, the distribution of FM, which may have clinical implications, can be examined. The original DXA technique did not distinguish between subcutaneous and visceral fat stores in the body; however, advances in analysis algorithms can provide DXA estimates of abdominal subcutaneous (SAT) and visceral (VAT) fat tissues by focusing on a specific abdominal region, just above the pelvis, analogous to CT and MRI imaging techniques described below. Thus, a whole-body DXA scan may now be able to provide fat distribution information similar to that obtained by more sophisticated imaging techniques, but at a much lower radiation dose and cost [206].

Methods based on body imaging techniques Anatomical imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) provide precise images which allow further regionalization of the three body compartments: FM, LTM, and BMC.

The CT technique use collimated beams of X-rays that are passed through the body and an array of detectors positioned on the opposite side of the body to detect the transmitted signal [186]. The X-ray source and detector assembly are rotated as a single unit around the body, and the data are collected and reconstructed to generate a cross-sectional image or "slice" of the body for each rotation. The physics of the CT procedure makes it a quantitative assay; that is, the relative density (g/cc) of each pixel in the cross-sectional image is obtained. Thus, anatomical regions such as the subcutaneous adipose tissue (SAT) layer, muscle, skin, internal organs, bone, and visceral fat deposits (VAT) can be identified. A disadvantage with routine CT imaging is that the radiation exposure is higher than that needed for DXA, and whole-body or extensive regional scans are not always practical [207]. The image requirements for a clinical CT scan can be relaxed when it is used for body composition analysis, such as for determination of VAT and SAT, which reduces the dose significantly [208]. The recent development of multislice CT scanners allows for capturing longer body regions in a shorter amount of time with the added benefit of reduced radiation exposure. The capability of using even thinner slices has improved resolution and allows investi-

gators to focus in greater detail on specific regions of interest [209].

Magnetic resonance imaging (MRI) provides internal images of the body that tend to be superior in resolution to those obtained using CT. One can easily identify the subcutaneous and visceral fat areas, for example, in an abdominal MRI image. However, the *quantitative* quality of the MRI image is much less than that obtained with the CT scan, and a whole-body MRI can take up to 10 times longer to perform than a DXA. Still, the MRI technique has several advantages such as the lack of exposure to ionizing radiation, and the system can be tuned to respond specifically to intramyocellular lipid within the LTM [210, 211]. This may enable a better understanding of the association of excess adiposity and intracellular lipid with pathophysiology [212].

Method Selection for Individuals with PWS

The pathogenesis of PWS involves alterations in body composition that are atypical for human physiology and pathophysiology. In particular, there is an inherent increase in FM that is disproportionate to LTM regardless of weight. LTM is extremely deficient, resulting in hypotonia and decreased spontaneous activity. The distribution of FM could be relevant to defining cardiovascular risk. Finally, BMD may be low, particularly in older individuals with PWS, increasing the risks for osteoporosis and fragility fractures. Medical treatment of PWS is largely focused on improving functional LTM, limiting FM and optimizing BMD. Given these considerations, body composition monitoring is an important element of clinical care for individuals with PWS and in PWS-related research. However, the selection of methods can be confusing.

As discussed above, there are several techniques that can be used to examine human body composition [186], each with its own sets of advantages and disadvantages. Two-compartment (FM, non-FM) and three-compartment (FM, LTM, BMC) models have been the most popular and clinically feasible. Higher-level models may provide a more complete picture of body composition, but multiple assays are required, some of which are not routinely found in most institutions.

In terms of two-compartment models, the BIA technique has become widely available partly because it is relatively easy to perform, requires minimum investment, and is portable, enabling routine clinical use and field studies. Unfortunately, the accuracy and precision of the body composition results may not be significantly better than those obtained using anthropometric measurements, such as body mass index calculations, waist circumference, or skinfold measurements.

For more accurate two-compartment modeling, air displacement plethysmography (i.e., using the BODPOD instrument) offers an attractive alternative to the more difficult underwater weighing technique [190]. However, the feasibility of this procedure in PWS has not been tested. In addition, although these methods for two-compartment modeling are designed to measure fat-free mass (with fat mass calculated as the residual), they have the disadvantage of not providing additional information regarding the non-fat component (i.e., BMC and LTM).

Table 6.2 summarizes key considerations for body composition measurement methods, classified by the measured component. Costs are based on 2020 US estimates. Precision and accuracy of each method are listed, as well as the minimal detectable change.

For practical purposes, the DXA procedure has become the reference method for the clinical assessment of bone mineral. This clinical acceptance of DXA, and its accessibility at many institutions, is also driving the use of this technique as a reference for the measurement of body fatness and lean mass. For patients with PWS, the DXA procedure has the additional advantages of rapidity, minimal patient cooperation requirements, and provision of measurements for all three clinically relevant body compartments. The 1% to 3% analytical precision of the DXA method allows detection of relatively small longitudinal changes in bone, fat, and non-bone lean tissues. However, there are significant differences in the

Table 6.2 Comparison of body composition methodologies

Measured compartment	Method	Method cost	Procedure[a] charge (US$)	Precision (%)	Accuracy (%)	MDC[b]amt. (%)
Total body water	BIA/ BIS	+	35	2–4	3–7	4 L (10)
	Dilution	++	50–100	1–2	2–3	2 L (5)
	QMR	++	–	1	–	1 L (3)
Fat-free mass	BIA/ BIS	+	35	2–4	2–8	4 kg (7)
	UWW	++	45	1–2	2–3	2 kg (4)
	ADP	++	40–80	1–3	2–3	2 kg (4)
	DXA	+++	70–180	2	1–2	1 kg (2)
Fat mass	QMR	++	–	1	3–5	1 kg (5)
	DXA	+++	70–180	2–3	3–5	2 kg (11)
	CT[d]	++++	300–600	3–4	3–4	– (10)
	MRI[d]	++++	500–1200	3–4	3–4	– (10)
Bone mineral density[c]	DXA	+++	70–180	1	2–3	0.04 g/cm^2 (4)
	CT	++++	300–600	1	1	1.2 mg/cc (1)

Method cost ranges (US$, based on 2020 US estimates): + <10K, ++ 10–100K, +++ 100–500K, ++++ >500K
BIA/BIS bioelectrical impedance analysis (single or multifrequency); *QMR* quantitative magnetic resonance; *UWW* underwater weighing; *ADP* air displacement plethysmography; *DXA* dual-energy X-ray absorptiometry; *CT* computed tomography; *MRI* magnetic resonance imaging
[a] Procedure charges will vary based on application (clinical, research) and insurance availability.
[b] Minimum detectable change (MDC) for an individual. Value in parenthesis is the change expressed as a percent based on body composition of a 79-kg male with 25% fat. For CT and MRI, a 10% change in either fat subcompartment should be detectable.
[c] DXA provides estimates of areal bone density (g/cm^2) for total body, spine, and hip. CT provides true bone density (mg/cm^3) for spine and extremities.
[d] CT and MRI provide regional composition values. Other methods provide whole-body values.

calculation of %FM by DXA versus more sophisticated techniques; therefore, further improvements in DXA may be needed before a consensus can be reached regarding the utility of DXA in estimating FM and non-bone lean mass [213]. In addition, DXA methodologies differ according to manufacturers; results are not directly interchangeable; and pediatric, age-related, and ethnic normal ranges have not been widely accepted [186, 214]. A minor disadvantage of DXA is that an exposure to X-rays is required; however, the dose is very small (<10 mSv) and carries minimal risk. From a practical standpoint, the DXA platform has some body weight limitations, often noted as 300 pounds for older units and 500 pounds for newer generation instruments.

Single-slice abdominal CT and MRI methods are excellent choices when information about the distribution of body fat in the abdominal region is important. This information could have relevance to defining cardiovascular risk. However, these methods have not yet been validated for monitoring of individual patients, PWS or otherwise, and are relatively costly and time-consuming. In addition, these methods do not provide information about whole-body tissue status. The more recent development of algorithms for VAT and SAT assessment by DXA may lead to increasing use of whole-body DXA over CT and MRI methods.

In summary, with the various techniques that are available today, it is possible to obtain an accurate in vivo assay of human body composition and to assess changes in clinically relevant body compartments to study the natural history of PWS and effects of treatment. Whole-body DXA is currently the most useful procedure for these assessments in individuals with PWS; however care should be exercised in the proper interpretation of results.

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7 Growth Hormone and Prader-Willi Syndrome

Aaron L. Carrel, Phillip D. K. Lee, and Harriette R. Mogul

In 2000, biosynthetic growth hormone (GH) became the first medication to receive regulatory approval for treatment of PWS. As of this writing, biosynthetic GH (somatropin and somatropin biosimilars) continues to be the only approved medication for PWS, with published evidence demonstrating significant benefits for children and adults with PWS [1]. This chapter presents a comprehensive review of relevant physiology and pathophysiology of the GH system and GH treatment efficacy and safety in PWS.

GH/IGF Axis Pathophysiology

Short stature is one of the cardinal features of PWS and was included in the initial description of the condition in 1956 [2] (see Chap. 24). Numerous studies have shown that growth is usually compromised during childhood and that the average final adult height is approximately 2 standard deviations below the mean for the reference population [3–11] (see Chap. 26). In individual cases, final adult height has been noted to be related to midparental height, i.e., PWS individuals with taller parents will be relatively taller than other PWS individuals [12]; however, final height is significantly less than midparental height. Although a proportion of children with PWS will have accelerated growth and normal stature during childhood, often in association with premature adrenarche, final adult height in these cases may be further compromised by the accelerated bone maturation. Thus, PWS is one of only a few conditions in which obesity is associated with short stature and is clearly distinguished from usual exogenous obesity, in which childhood linear growth is accelerated and final height is normal or increased [13].

Deficient serum GH levels during standard stimulation test procedures have been reported in most children [3, 14–23] and adults [24–26] with PWS. However, these results have been met with skepticism since GH levels are not low in all individuals with PWS despite short stature and GH levels are often low in non-PWS obesity that is not associated with short stature [27].

GH is synthesized in the anterior pituitary gland and released episodically into the bloodstream. GH itself is thought to have minimal, if any, effect on somatic growth. Instead, GH stimulates synthesis of other growth factors in liver and other tissues. These growth factors then act

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to stimulate growth of body tissues, including bone and muscle.

One of the primary growth factors that mediate the GH effects is insulin-like growth factor-I (IGF-I). In classical GH deficiency, IGF-I levels are very low, and this is associated with decreased linear growth. On the other hand, in common exogenous obesity with normal height, GH levels are low, but IGF levels are usually normal or elevated [27].

IGF-I is carried in the bloodstream by several specific binding proteins, including IGFBP-3. Therefore, measurement of either serum IGF or serum IGFBP-3 levels provides an indirect measure of GH secretion and a direct measure of the GH/IGF axis. Reliable laboratory assays were developed for IGF-I in the mid-1970s and for IGFBP-3 in the mid-1980s. Since then, IGF-I and IGFBP-3 levels have been reported to be abnormally low in both children and adults with PWS [14, 19, 24, 28–32]. The combination of low GH and low IGF-I argues for the existence of a deficiency in the GH/IGF axis in PWS [33, 34].

GH/IGF axis deficiency is also suggested by the body composition characteristics in PWS. As discussed in the preceding chapter, both fat and lean mass compartments are increased in common exogenous obesity. However, in PWS, fat mass is preferentially increased [35–37], a condition that is found in other conditions with GH deficiency [38].

GH (*aka* somatotropin) is secreted by specialized cells, or somatotropes, located in the anterior pituitary gland and released into the bloodstream in an intermittent pattern, with each burst having a relatively short circulating half-life. The pattern of these bursts is regulated by a complex system involving inhibition of GH release by intermittent secretion of somatostatin (inhibitory) and GH-releasing factor (stimulatory) from the arcuate nucleus of the hypothalamus, coupled with negative feedback signals from the periphery to the CNS [39]. Larger bursts of GH release are observed during fasting, exercise, sleep, and during puberty. Between these bursts, GH levels are normally low.

Because of this episodic secretion, random GH levels have limited utility in the assessment of GH adequacy since such measurements are likely to be low. Therefore, various testing protocols are used to predictably stimulate GH secretion, using physiologic (e.g., fasting, monitored exercise) and/or pharmacologic (insulin-induced hypoglycemia, clonidine, arginine, ornithine, L-DOPA, glucagon, macimorelin) stimuli followed by serial blood sampling.

Although provocative GH testing has been a widely accepted diagnostic procedure for many decades, there is considerable controversy regarding reliability and clinical utility [40, 41]. A large proportion of individuals will fail to achieve a normal GH peak on one test but not another, resulting in a requirement for two or more tests. In addition, individuals who fail testing in childhood may have a normal response when tested at a later age. Furthermore, there is lack of agreement on the definition of a "normal" provoked peak GH response level, with published criteria ranging from <3 to 15 ng/mL for childhood GH deficiency, and this is complicated by considerable variability between assay methods [42].

Finally, there are questions regarding the physiologic relevance of GH secretion. GH is a major factor that stimulates secretion of growth-promoting factors such as IGF-I; however, other factors are involved. For instance, in some individuals who have GH deficiency due to craniopharyngioma, IGF-I levels and height growth are normal [43]. The etiology of this condition of "growth without growth hormone" is incompletely defined but has been related to hyperphagia and obesity, with high insulin levels stimulating IGF-I synthesis. In addition, children with short stature and growth failure may have low IGF-I levels despite normal or high GH levels; the extreme example of this situation involves defects in the GH receptor. Therefore, although very low GH levels are indicative of pituitary dysfunction, neither high nor low levels are necessarily predictive of IGF-I levels or height growth patterns.

It is evident that most individuals with PWS have a deficiency in IGF-I and characteristics of GH deficiency, although many patients will have apparently normal stimulated GH levels. The specific reasons for this discordance in PWS are not entirely known. However, several points should be considered:

1. There is no evidence for GH resistance as might be observed with GH receptor defects. GH levels

are not elevated, and a therapeutic response is seen with usual GH replacement therapy.
2. There is no evidence for a defective IGF-I synthesis in response to GH; IGF-I levels increase during GH replacement therapy.
3. The low GH levels could be related to obesity, as is seen with exogenous obesity. In this latter situation, inhibition of GH secretion may be due to excess free fatty acids [44]. Free fatty acid levels in PWS are similar to body mass index (BMI)-matched controls [22, 45–48] which could explain the low GH levels; however, this does not explain the discrepancy in IGF-I levels between PWS and non-PWS obese individuals. It should also be recalled that BMI, which is used as a surrogate measure of body fat in such studies, may underestimate fat mass in PWS relative to obese controls with similar BMI. Arguably, free fatty acid levels may be lower in individuals with PWS if fat mass were more precisely matched.
4. GH deficiency in PWS has been attributed to intrinsic hypothalamic dysfunction; however, there are no definitive data in support of this hypothesis nor for the alternate hypothesis of a defect in peripheral signaling [49].
5. GH levels are normal in a significant proportion of individuals with PWS implying that there is no intrinsic defect in pituitary GH synthesis specifically associated with the syndrome. However, GH testing is acknowledged to be non-physiologic [40, 41]; therefore, the possibility of a defect in endogenous (i.e., natural) pituitary GH secretion cannot be completely excluded. Low levels of IGF-I could be due to low total daily secretion of GH despite normal stimulated levels.
6. Unlike in the condition of "growth without growth hormone" described above, individuals with PWS had low insulin levels [29], with a lack of evidence for insulin resistance, despite hyperphagia and obesity.

In summary, short stature and body composition abnormalities in individuals with PWS, including increased fat mass and decreased lean mass, are consistent with a defect in the GH/IGF axis [33, 34]. Although the exact mechanisms have not been delineated, an insufficient production of IGF-I is evident in most cases. The composite data indicate that a complete defect in pituitary GH synthesis may not be involved, although stimulated GH levels are low in a considerable proportion of cases.

GH Therapy

GH was first identified in the 1920s, with purification of primate GH achieved in the 1950s [50]. Therapeutic use in a child with GH deficiency was first reported in the late 1950s. Until 1985, GH was available only as a purified preparation from animal sources and human cadaver donors, and non-primate GH was found to be relatively ineffective in humans. National programs to collect donated human cadaver pituitary glands and purify GH for therapeutic use were initiated in the USA in 1963 and shortly thereafter in other countries. This very limited, sporadic supply was distributed gratis to GH-deficient children through an application and approval process. In 1978, commercial supplies of cadaver-derived human GH became available.

In 1985, a case of Creutzfeldt-Jakob disease, a fatal neurodegenerative disorder, was reported in a patient who had received cadaver-derived human GH [51]. Other cases were identified worldwide and were suspected to be due to transmission of an infectious agent in the cadaver-derived GH preparations. Cadaver-derived GH was immediately removed from clinical use and replaced by biosynthetic GH, manufactured through recombinant DNA technology. Creutzfeldt-Jakob disease was later confirmed to be due to a transmissible agent, called a prion, which was present as an impurity in the cadaver-derived GH preparations.

When it was precipitously released into the marketplace in 1985, biosynthetic GH had not yet gone through complete safety and efficacy trials. Therefore, a procedure for post-marketing surveillance was established by agreement between the GH manufacturers and the US Food and Drug Administration. In 1987, Genentech Inc. established the National Cooperative Growth Study (NCGS) in the USA, and Kabi Pharmaceuticals (now Pfizer) established the Kabi International Growth Database (KIGS). Since then, post-

marketing studies have become a requirement for new pharmaceuticals in the USA and throughout the world, providing information regarding safety and efficacy of prescription medications.

The increased supply of GH opened the doors for treating conditions other than childhood GH deficiency, including a number of conditions that do not necessarily involve GH deficiency, guided primarily by treatment efficacy and risk/benefit considerations. In addition to PWS, other US FDA-approved indications and the year of approval include childhood Turner syndrome (1996), childhood growth failure due to chronic renal failure (1997), HIV-associated wasting in adults (1998), adult GH deficiency (1998), childhood PWS with growth failure (2000), childhood growth failure in children who were small for gestational age at birth (2001), childhood severe idiopathic short stature with abnormally low predicted adult height (2003), patients with short bowel syndrome who require nutritional support (2003), childhood growth failure due to *SHOX* haploinsufficiency (2006), and growth failure in children with Noonan syndrome (2007). It should be noted that the European regulatory labeling for the use of GH in PWS is "for improvement of growth and body composition in children," while the US labeling specifies "long-term treatment of pediatric patients who have growth failure due to Prader-Willi syndrome" without mention of other important beneficial effects. Labeling in other countries tends to follow the European indications.

Effects of GH Treatment in Prader-Willi Syndrome (Figs. 7.1 and 7.2)

Height and Other Skeletal Growth

Studies of GH treatment in PWS confirmed that GH treatment increases growth rate children with PWS [14, 30, 31, 36, 52–54]. Longer-term studies (2–5 years) have provided strong evidence of a significant and sustained growth response to GH treatment [1, 55]. Favorable effects on growth were noted in a Swedish study of 18 children with PWS treated with GH for 5 years [56]. A Swiss study of 23 PWS children treated with GH for a median of 3.5 years showed an increase in mean height standard deviation score (SDS) of 1.8, with adult height predictions approaching midparental target height [57]. Longer-term data demonstrate normalization of final adult height [58, 59].

In a randomized, controlled trial, height velocity increased from −1.9 to +6.0 SDS during the first year of GH administration (0.1 IU/kg/day) in children with PWS, compared with a decrease from −0.1 to −1.4 SDS in the no-treatment control group [32]. For the treatment group, this corresponded to a mean growth rate of approximately 12 cm/year, which is greater than that observed for virtually all other conditions treated with GH.

In addition to increased height velocity, small hands and feet (acromicria), a typical characteristic of PWS, improved toward normalization in children with PWS during GH treatment [60, 61]. Normalization of head circumference has been reported in infants with PWS who received GH treatment [54, 62].

Standardized growth curves based on data from 171 children with PWS who received GH treatment demonstrate marked improvement in height and weight compared to previous charts based for non-GH-treated children [63].

Body Composition and Metabolism

GH treatment of GH-deficient children without PWS not only restores linear growth but also promotes growth of lean body mass, decreases fat mass by increasing fat oxidation and total body energy expenditure, increases bone mineral density following an initial period of increased bone resorption, and improves cardiovascular risk factors [64, 65]. Children with PWS respond to GH therapy with similar improvements in body composition and metabolism, and these effects may be more clinically important than change in growth velocity.

Increased lean body mass and bone density have been reported in several uncontrolled studies of GH therapy in children with PWS [36, 60, 66, 67], although declining bone mineral density relative to a reference population has been reported during long-term GH treatment [68]. Favorable effects to reduce absolute or percent body fat have also been reported, although these effects are less

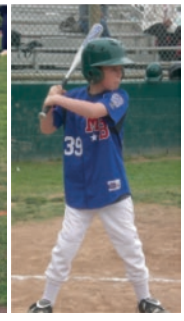

4 months old


6 months old, with parents

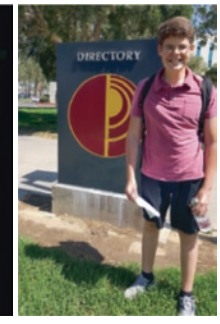

12 months old, 3 months after starting growth hormone treatment


3 years old


6 years old

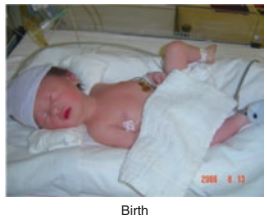

10 years old


15 years old
Saxophone recital



18 years old
First day of college


21 years old, with father
continuing growth hormone treatment

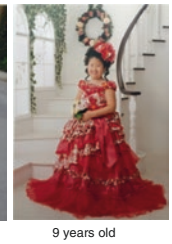

Birth


6 months old


10 months old


16 months old; 4 months after starting growth hormone treatment


4 years old


9 years old


12 years old

13 years old


15 years old (far left) with parents and siblings

Figs. 7.1 and 7.2 Individuals with PWS who were treated with GH starting in early childhood (Published with permission)

consistent than for improvement in lean body mass [14, 36, 60] as may be expected due to the overall variability in calorie intake, energy output, and body weight in the general population.

In a controlled trial of children with PWS, dramatic improvements in lean body mass, bone density, and linear growth were demonstrated in the GH-treated group (1.0 mg/m^2/day) as compared with an untreated control group over the first year [69]. Fat utilization was also increased, while percent body fat stabilized or decreased in most subjects. Over subsequent years of the study, in which the untreated group was crossed over into GH treatment, progressive increases in lean body mass

and linear growth and continued beneficial effects on body fat were observed [61, 70, 71].

In the same study, a dose response was noted during the dose-ranging study at 24–48 months [72]. During this study period, continued progressive increases in lean body mass and height improvement and stabilization of percent fat occurred with administration of either 1.0 mg/m^2/day or 1.5 mg/m^2/day of GH, but not with a lower dose of 0.3 mg/m^2/day. Prior improvements in bone mineral density were sustained regardless of dose. The GH treatment responses in children with PWS are greatest during the first 12 months, as is typically observed for other types of childhood GH treatment. The rates of positive changes in lean body mass and bone mineral density slowed but did not regress during more prolonged GH therapy at doses ≥1.0 mg/m^2/day and continued to be higher than expected compared with reference data for healthy children without PWS.

Given their reduced lean body mass, children with PWS would be expected to demonstrate markedly reduced resting energy expenditure (REE). Prior to GH treatment, children with PWS showed reduced REE compared with predicted values for non-PWS children matched for surface area (22.4 ± 4.4 kcal/m^2/h versus 43.6 ± 3.2 kcal/m^2/h; $p < 0.0001$) [72]. GH therapy increased REE in children with PWS in parallel with changes in lean body mass, with a similar dose dependence, i.e., effects were noted at both 1.0 mg/m^2/day and 1.5 mg/m^2/day of GH but not with a lower dose of 0.3 mg/m^2/day.

GH deficiency is associated with lipogenesis and fat storage predominating over the accretion of lean mass, even in the absence of overt obesity. Preference for fat utilization as an energy source is reflected in a reduction of respiratory quotient (RQ). The RQ normally ranges from 0.7 (strong predominance of fatty acid oxidation) to 1.0 (exclusive oxidation of carbohydrate) to >1.0 (indicating lipogenesis from carbohydrate). GH treatment in PWS children was associated with a decrease in RQ values, indicating increased utilization of fat for energy [72]. Thus, compared with non-GH-treated PWS controls, GH-treated PWS patients demonstrated a shift in energy derived from oxidation of fat, coincident with reductions in fat mass. Similar results have been obtained in another randomized, controlled GH treatment study of children with PWS [62].

Muscle and Respiratory Function

Deficient muscle mass, hypotonia, and respiratory dysfunction are major contributors to morbidity and mortality in PWS. GH therapy improves lean body mass, and, more importantly, this is accompanied by improvements in physical strength and function.

Anecdotal reports of improvements in physical stamina, strength, and agility were reported in the initial experience with GH treatment of children with PWS. Parental reports included a variety of new gross motor skill, e.g., independently climbing up the school bus steps, carrying a gallon carton of milk at the grocery store, participating in a normal gym class without restrictions, and being able to join a karate class [73]. Such observations provided impetus for more rigorous investigations of these effects.

Improvements in physical strength and agility were carefully documented in a randomized, controlled study using objective measurements of muscle strength and function, including a timed run, sit-ups, and weight lifting [72]. Significant improvements in running speed, broad jump distance, number of sit-ups, and number of arm curls were documented after 12 months of GH treatment compared with controls. During 4 years of GH treatment, improvements in broad jumping and sit-ups were maintained, while further improvements were noted in running speed and arm curls. PWS children still scored well below the non-PWS children for all parameters studied; however, the improvements in strength and agility were associated with significant functional benefits.

Similar positive results on body composition and resting energy expenditure have been reported in a 12-month double-blind, placebo-controlled, randomized crossover GH treatment study of 12 children with PWS [74].

Chest wall and oropharyngeal hypotonia are likely to be major contributing factors to breathing and respiratory dysfunction in PWS. Significant improvements in minute ventilation, airway occlusion pressure, and ventilatory response to CO_2

were reported after 6–9 months of GH treatment in nine children with PWS [75]. In the randomized, crossover study discussed above [74], significant improvements in peak flow rate, vital capacity, and forced expiratory flow rate were observed after 6 months of GH treatment. In addition, the number and duration of apneic events tended to decline. In 20 children with PWS involved in a longitudinal study of GH therapy, significant improvements in respiratory function were seen after 1 year of therapy and were sustained at retesting after 24 months of therapy [61, 72]

Due to ethical concerns, none of the studies of GH treatment in children with PWS included a control group for longer than 12 months. Therefore, the impact of long-term GH-related change on the natural history of PWS has been addressed by comparing a cohort of children with PWS treated with GH for 6 years, beginning at a mean age of 13 months, to a similarly aged cohort of children with PWS naïve to GH treatment [76]. As compared to the treatment-naïve group, the GH-treated cohort was significantly taller (mean 131 versus 114 cm) and had significantly lower percent body fat (mean 36.1 versus 44.6%) and higher lean (e.g., muscle) mass (24.1 versus 16.7 kg) as assessed by dual X-ray absorptiometry. In addition, the treatment group had significant greater motor strength as assessed by standing broad jump (22.9 versus 14.6 inches) and number of sit-ups in 30 s (12.4 versus 7.1). These results demonstrate a positive effect of childhood GH treatment on the natural history of PWS and validate the previous anecdotal reports (Figs. 7.1 and 7.2).

Behavioral Effects and Quality of Life

Parents often offer anecdotal reports of improvement, particularly in relation to eating behavior, alertness, and ability to concentrate. In addition, one might suspect that improved motor function would be associated with improvements in school performance and social functioning. The impression of increased alertness and activity has been reported in uncontrolled studies of GH therapy in PWS [60]. A short-term study demonstrated improvements in behavior during GH treatment in children with PWS, which regressed during treatment withdrawal [77].

Children with PWS have mild to moderate cognitive impairment. A few short-term studies have shown positive effects of GH treatment on cognitive development but have limited ability to distinguish improvement from lack of decline in cognition. A long-term study involved children with PWS treated with GH for 8 years, starting at a mean age of 8.1 years old, with cognitive function assessed periodically using the Wechsler Intelligence Scale for Children (WISC; Vocabulary, Similarities, and Block Design subtests), with calculation of total intelligence quotient (TIQ) [78]. Block Design improved during the monitoring period; overall cognitive ability remained constant and similar to the non-PWS to the reference Dutch population. An untreated comparison group was not available; however, earlier studies had suggested a decline in cognitive measures without GH treatment.

In a randomized, controlled study of GH treatment of children with PWS (control group crossed over the treatment after 1 year), 27 GH-treated subjects and 14 untreated control subjects had behavioral assessments at 6-month intervals using a modified Offord Survey Diagnostic Instrument, which includes behavioral checklist and parental questionnaire sections [79]. Behavioral checklist results showed no statistically significant differences for between-group effects on multiple measures of psychological and behavioral function. However, within-group analysis showed a significant reduction of depressive symptoms only in the GH treatment group after 1 year, with the effect maintained at 2 years. In the under-11-year-old group, a significant increase in attention-deficit/hyperactivity symptoms was observed with GH treatment, perhaps in agreement with the anecdotal reports of increased alertness. In the questionnaire section, parents reported improved school performance, memory, and family/social relationships with GH therapy.

A meta-analysis of GH treatment of PWS [1] revealed three randomized studies that evaluated quality of life, all relatively short term (<2 years), with one study showing a positive result [80] and

two showing no impact, positive or negative [81, 82]. A separate meta-analysis showed that there was no published evidence of a GH treatment effect on cognitive or behavioral development [83].

Infants

Infants with PWS suffer considerable morbidity related to hypotonia, including feeding and respiratory impairment. Increased body fat and decreased lean mass have also been demonstrated, even in infants with PWS who are underweight [84, 85]. However, deficits in linear growth may not be evident until after 12–24 months of age.

GH treatment of infants with PWS have shown beneficial effects on growth, body composition, muscle function, and motor development [73, 86–90]. In a randomized, controlled study of GH treatment in 25 infants with PWS (mean 15.5 months old), a significant increase in lean mass and a decrease in fat mass (both measured by dual X-ray absorptiometry) was observed after 6 months of GH treatment [85, 91]. Age-equivalent motor scores, assessed using the Toddler Infant Motor Evaluation (TIME), increased approximately twice as fast in the treatment group. Dramatic increases in head circumference within the normal range were noted in the treatment group with no evidence of CNS pathology; this increase presumably represents increased brain growth.

A randomized, controlled study in 34 infants with PWS showed decreased percent body fat, and improved motor and cognitive development, after 1 year of GH treatment [92]. After 8 years of GH treatment, children with PWS who started treatment before 2 years old (mean 1.4 years old) scored significantly higher than children who started treatment in later childhood (mean 8.1 years old) on the WISC Vocabulary subtest and had a significantly higher calculated TIQ [78].

These observations emphasize the importance of diagnosing PWS in infancy and starting GH treatment as soon as it is feasible, preferably before 2 years old. The benefits of early diagnosis and treatment also provide an argument for inclusion of PWS in newborn screening programs [93].

Older Children and Adults

As discussed in preceding sections, GH treatment provides multiple benefits for children with PWS. However, treatment efficacy is usually monitored by measuring height growth. After cessation of linear growth, questions have been raised regarding continuing GH treatment in adults with PWS.

Since GH replacement therapy does not yet have specific regulatory approval for treatment of adult PWS, formal testing of the GH/IGF axis GH secretion may be necessary to meet the treatment indication of adult GH deficiency, despite the controversies regarding the physiologic and clinical relevance of such testing. Studies indicate that adults with PWS have GH/IGF axis deficiency, as a continuation of the condition that begins in childhood [24, 25], particularly low IGF-I levels. Stimulated GH levels are usually low, particularly if childhood standards are used, but as with pediatric PWS, GH responses are highly variable with a significant proportion having levels above the selected boundary despite having a low IGF-I level [26, 94, 95]. For non-PWS adult GH deficiency, a typical boundary for a provoked GH level is 5 ng/mL, while 10 ng/mL is often used for children.

The optimal agent to use for provocative GH testing in adults is controversial [96, 97]. Pro and con arguments relating to safety, validity, and reliability (reproducibility) can be given for virtually all secretagogues commonly used, including clonidine, L-DOPA, propranolol, pyridostigmine, arginine, GH-releasing factor and analogues, glucagon, and insulin. Secretagogue selection is further complicated in adults with PWS in view of the potential interaction of obesity, gonadal steroid deficiency, and the presumed hypothalamic level of the GH secretory defect. L-DOPA and other dopaminergic stimuli may act to stimulate pituitary GH secretion by augmenting hypothalamic production or release of GH-releasing factor, in

contradistinction to another commonly used secretagogue, arginine [98].

Measurement of IGF-I might be a useful initial screening test to predict a low provoked GH level, a level that is below the age-specific reference range [96]. In addition, treatment of adult GH deficiency is often guided by monitoring of IGF-I levels; therefore, a low level is expected before initiation of GH treatment.

Overall, adults with PWS have a continuation of the GH/IGF axis dysfunction that has onset in childhood, with variable GH levels depending on assessment method and other factors and a low IGF-I level regardless of GH levels. An integrated assessment of the GH/IGF axis, rather than reliance on GH testing, has been suggested for adults with PWS [95].

Adults with PWS have signs and symptoms similar with childhood PWS and overlap GH-deficient adults without PWS, including increased body fat, decreased lean mass, hypotonia, osteoporosis, and fatigue. Beneficial effects of GH treatment on body composition, muscle function, and other measures have been demonstrated in numerous studies of adult PWS regardless of GH test results [26, 99–108]. However, although GH treatment has been universally accepted as a treatment for childhood PWS, GH treatment of adults with PWS is less widely accepted [109].

There may be special considerations involved with GH replacement therapy in adults with PWS:

1. PWS adults may not have received GH therapy in childhood, raising questions regarding adverse effects of initiating GH replacement therapy in treatment-naïve adults. However, published studies in adults have not revealed any unique concerns.
2. The presence of concomitant untreated hypogonadism could exacerbate the manifestations of GH deficiency.
3. The co-existence of significant medical conditions, including morbid obesity, scoliosis, insulin resistance, Type 2 diabetes mellitus (T2DM), and cardiovascular disease may require additional surveillance during GH treatment.
4. Cognitive, behavioral, and social considerations could complicate both initiation and long-term administration of GH injections. The specialized living situations of many PWS individuals may be a limiting factor.

Thus, adults with PWS have a wider spectrum for both potential benefit and risk than do other adults with GH deficiency. Recent reviews of GH treatment for adults with PWS concluded that GH treatment is safe and well tolerated, and results in beneficial body composition changes [110–112].

Pretherapy Testing

Since most children with PWS will meet requirements for GH use, formal testing of GH secretion is not usually necessary prior to therapy. However, such testing may be indicated in a few instances:

1. In the USA, GH therapy is specifically labeled for treatment of PWS *with growth failure*, rather than for body composition abnormalities associated with PWS. In some cases, growth failure per se may be difficult to document. For instance, as previously described, children with PWS and premature adrenarche may have relatively accelerated linear growth but compromised final height. In such cases, GH testing may be useful to document the alternate therapeutic indication of GH deficiency.
2. In utero and neonatal problems, including prematurity and hypoxia, are known risk factors for pituitary GH deficiency and panhypopituitarism (i.e., GH deficiency plus other pituitary hormone deficiencies, such as TSH and ACTH). Infants with PWS who suffer these types of problems should be considered for a complete pituitary evaluation, including measurement of GH levels, since multihormonal replacement and brain imaging may be necessary. Unexpected neonatal hypoglycemia may be a warning sign of hypopituitarism; low GH and/or cortisol levels measured during hypoglycemia can be diagnostic for pituitary deficiency.

Another problematic situation is the neonate with PWS. Since evidence suggests that GH replacement may be beneficial for brain growth and neuromotor development, it may be clinically unwise to withhold therapy while awaiting documentation of growth failure. Consultation with a pediatric endocrinologist with experience in the treatment of neonatal PWS is highly recommended.

Other specific testing that may be considered for children with PWS prior to therapy includes the following:

1. Thyroid function testing (T4, TSH). Although thyroid abnormalities do not occur with increased frequency in PWS, thyroid problems are common in the general population and, if untreated, may have detrimental effects on neonatal development as well as limit the efficacy of GH therapy at all ages.
2. Fasting blood glucose and/or glycated hemoglobin (hemoglobin A1c). Elevations in either of these levels may indicate impaired glucose tolerance or Type 2 diabetes mellitus, either of which may be exacerbated by GH therapy.
3. Bone age radiograph may be used to estimate growth potential and calculate a predicated adult height, particularly if the bone age is >6 years.
4. Liver enzymes to assess for hepatic steatosis and renal function tests (urea nitrogen and creatinine), if clinically indicated.
5. Dual X-ray absorptiometry to assess hip and spine density, preferably in combination with a whole body scan to assess body composition.
6. Scoliosis radiographs, if clinically indicated.

Whenever feasible, formal baseline testing of motor function should be documented for comparison purposes. Video documentation may also be considered.

For adults with PWS, other recommended tests prior to GH therapy are similar to those listed above for children with PWS, with these exceptions/additions:

1. Bone age radiographs are not indicated in adults since they have already achieved epiphyseal closure.
2. Since scoliosis may progress during adult life, appropriate radiographs should be obtained, if clinically indicated.
3. As mentioned above, IGF-I level(s), used for therapeutic monitoring, should be obtained and should be low prior to treatment.
4. Because height growth cannot be used as a somatic efficacy measure, baseline dual X-ray absorptiometry scan, preferably with a whole body scan in addition to hip/spine bone mineral density, is highly recommended.
5. Adults may be at an increased risk for glucose intolerance and Type 2 diabetes mellitus. Therefore, consideration should be given to inclusion of a HbA1c level or oral glucose test prior to initiation of GH therapy.
6. Consideration should be given to a baseline prostate-specific antigen (PSA) level in males and PAP smears and mammograms in females.
7. A baseline quality-of-life assessment may also be useful.

Childhood GH Therapy

In general, GH therapy for children with PWS follows the same course as for other conditions. Monitoring of linear growth rate, growth potential (e.g., bone age radiographs), and weight serve as the primary indicators of therapeutic effect and need for dose adjustment. However, while somatic growth is an important effect of therapy, the beneficial effects of GH on body composition and physical function are of greater importance in children with PWS. In this sense, height growth serves primarily as an obvious surrogate marker for overall therapeutic efficacy, including body composition. In Europe and other regions, improvement in body composition is an indication for GH treatment of PWS; therefore, consideration should be given to monitoring of body composition (e.g., whole body dual X-ray absorptiometry).

Labeling for GH use in children with PWS states that "a dose of 0.24 mg/kg body weight/week is recommended" or 0.034 mg/kg/day; labeling may also include the alternate dose calculation of 1.0 mg/m^2/day based on body surface

area. This recommendation is apparently based on data from Europe, where GH doses used are generally lower than in the USA for all treated conditions. In a review of 15 sets of studies relating to GH use in PWS, Eiholzer [73] found doses ranging from 0.02 to 0.05 mg/kg/day. The highest reported doses (0.04–0.05 mg/kg/day) were in some of the earliest reports [14, 30, 36], and one of the authors (PDKL) has continued to use a standard dose of 0.05 mg/kg/day for all pediatric patients with PWS. Another author (ALC) has coauthored studies regarding GH dose response in PWS [72].

Controversy over GH dosage in PWS is mirrored by similar discussions in non-PWS conditions [113]. Although GH therapy has been in use for over 50 years and biosynthetic GH was released in 1985, surprisingly few data have been published regarding optimal dosage for any condition. In most studies related to dose response, the maximal measured response occurs at the highest dose tested, which is the case in relation to GH effects on body composition in children with PWS [72]. Even for a straightforward endpoint such as height growth in non-PWS GH-deficient children, optimal dosage has not been defined, although it is clear that for a given weekly dosage, daily administration is more efficacious than a less frequent dose interval and that increased efficacy is not necessarily proportionate to increased dose [113]. Indeed, the average dose used for treatment of childhood GH deficiency, 0.3 mg/kg/week (0.043 mg/kg/day), evolved primarily from composite practice experience and is higher than some manufacturer labels for this indication. Higher weight-based doses have been recommended for children with Turner syndrome (0.375 mg/kg/week), growth failure associated with chronic renal failure (0.35 mg/kg/week), small for gestational age children with failure of catch-up growth (0.48 mg/kg/week), and for "pubertal dosing" of GH-deficient children (0.7 mg/kg/week), all primarily based on doses selected for the preapproval clinical trials.

Efforts to define individualized upper-dose limits based on IGF-I levels are complicated by high inter-assay and inter-lab variability, intraindividual physiologic variability, age- and sex-dependent normal ranges, and extremely wide normal ranges, especially during puberty. In addition, long-term efficacy data based on IGF-I or other biochemical response markers are not available. There are virtually no data relating IGF-I levels to dose-related adverse effects within the usual prescribed ranges for GH. However, many clinicians choose to monitor IGF-I levels during GH treatment.

For PWS, an argument has been made that dosing should be based on lean mass rather than on total body weight. However, this would require accurate determination of lean mass at each visit, and there are no data to support the effectiveness of such an approach.

A prudent approach to GH therapy in children with PWS may be to use a starting dose that is at the labeled recommendation of 0.24 mg/kg/week (0.034 mg/kg/day, based on total body weight) but not to exceed the highest published efficacious dose (0.35 mg/kg/week, or 0.05 mg/kg/day).

Height is a reasonable measure of clinical efficacy for GH treatment in children with PWS, although other treatment effects may be equally important. As observed in other GH-treated populations, for a given weight-based dose the height velocity will be greatest during the first year of therapy, typically into supranormal ranges; this may be due to "catch-up" growth. This is often followed by a decrease into essentially normal height velocity ranges, transient augmentation with initial sex-steroid replacement, and eventual attainment of a final adult height.

Other clinical parameters that should be monitored during childhood GH therapy include the following:

1. Body fat: Although numerous studies indicate that GH therapy may significantly reduce body fat in children with PWS, this effect is not universal. GH therapy may augment accretion of body fat in children who do not have a controlled diet. Assessment of body fat should involve a clinical exam, as well as measurements of weight and calculation of BMI, acknowledging that BMI can also reflect increased lean mass. Periodic quantitative or

semiquantitative measures of fat may be useful; bioelectrical impedance is a typical method.
2. Head circumference, particularly in infants to 3 years old: Failure of head growth should raise suspicions of craniosynostosis, especially if the fontanels are prematurely closed; this disorder requires immediate evaluation. In cases with an exuberant increase in head growth, hydrocephalus can usually be excluded by careful clinical examination, although cranial imaging will be required for confirmation. Widely spaced sutures and/or a bulging anterior fontanel should be cause for concern and further evaluation.
3. Back curvature: Scoliosis is a common occurrence in PWS, and an abnormal curve may worsen during rapid growth. It should be emphasized that GH therapy is not thought to cause scoliosis in PWS, and there is no current evidence for stopping GH therapy because of this condition. Close coordination with orthopedic care is needed. A significant scoliotic curve should also be considered when monitoring height.
4. Bone age radiograph: An annual hand/wrist radiograph for determination of bone age was formerly a standard practice during childhood GH treatment. The primary utility of a bone age is for estimation of epiphyseal closure and further growth potential (i.e., final adult height potential). To avoid unnecessary radiation exposure, it may be best to limit bone age radiographs to situations where there is a concern regarding further growth potential. It should also be remembered that height is determined by growth of the vertebrae, hips, and legs—these epiphyses typically close after those of the hand. Therefore, bone age radiographs should always be interpreted together with actual measurements of height velocity.
5. Dual X-ray absorptiometry: Although whole body dual X-ray absorptiometry provides useful research information regarding changes in body composition, its role in clinical monitoring of childhood GH therapy is not clear, and routine use is not currently recommended [114]. Hip and vertebral measurements are useful for diagnosing and monitoring osteoporosis, if clinically indicated.
6. Laboratory testing: At the current time, there is no evidence to support *routine* monitoring of IGF-I, IGFBP-3, thyroid function tests, glucose tolerance, hemoglobin A1c, or other laboratory tests during GH therapy of children with PWS. Of course, such tests may be indicated in individual cases based on signs and symptoms, and an individual physician may have his or her own routine monitoring guidelines based on personal experience and opinion.
7. Whenever possible, muscle function, physical activity, school performance, and quality-of-life measures should be monitored.

GH therapy for children with PWS is usually continued until attainment of final adult height. It should be noted that height growth may continue after apparent closure of hand and wrist epiphyseal centers (i.e., on a typical bone age radiograph), since the hip, knee, and vertebral epiphyses tend to mature more slowly than the distal centers. Patients are usually seen in clinic at 3- to 4-month intervals for dose adjustments and monitoring. Lack of significant height gain (after correcting for the effects of scoliosis) over two visit intervals (or approximately 6–8 months) may be an indication for cessation of childhood GH therapy and consideration for transitioning to the adult GH therapy regimen.

The issue of how to optimally transition GH-deficient individuals from childhood to adult therapy is somewhat controversial, with some practitioners recommending immediate transitioning and others advocating cessation of GH therapy and periodic reevaluation of GH/IGF status and body composition [115]. Limited experience suggests that some individuals with PWS can have a rapid reversal of body composition benefits with GH cessation. In all cases, careful monitoring during the transition period is essential.

Adult GH Therapy

The clinical goals of GH therapy in adults with PWS include improvements in (1) body composition, with reduction of fat mass and increase in lean mass, (2) lipid profiles, (3) bone density, and (4) quality of life. In addition, as with treatment of children with PWS, improvement in muscle function is also a desirable outcome.

In contrast to childhood GH therapy, where GH dosing is based primarily on body size (weight or surface area) and growth response, GH dosing in adults is typically administered in a fixed amount (mg/day) with adjustments based on laboratory measures of response. In adult patients with adequate nutritional status and normal liver function, the serum IGF-I level is used as a surrogate measure of GH adequacy.

For adults with GH deficiency, a typical starting dose is 0.1–0.2 mg/day, without adjustment for weight or surface area. When corrected for a typical adult weight, this dose is several-fold lower than in children. Subsequent dose changes are often based on routine measurements of IGF-I at 1- to 6-month intervals, with GH dose changes in 0.1–0.2 mg/day increments/decrements to achieve an IGF-I level within 0 to +1 standard deviation of age- and sex-specific normal ranges. Experience suggests that a typical stable dose to maintain normal IGF-I levels is 0.6–1.0 mg/day for adults with PWS.

In general, IGF-I should be measured approximately 1 month after a GH dose change. It should be noted that IGF-I levels show considerable variability based on assay methodology and laboratory. Therefore, it is important to select a single laboratory with good reference ranges and quality control procedures.

Other parameters to be monitored during adult GH therapy include the following:

1. Body fat. The same considerations as discussed for children. Bioelectrical impedance assessment can provide a reasonably objective estimate of body fat.
2. Back curvature.
3. Dual X-ray absorptiometry. Osteoporosis is a major cause of morbidity in adults with PWS; therefore, regular measurements (every 1–2 years) of hip and spine bone mineral density are recommended.
4. Polysomnography and/or pulmonary function testing may be indicated in individual cases.
5. Laboratory testing. Annual fasting lipid panel, fasting glucose, hemoglobin A1c, and general chemistry profile (including liver enzymes) may be recommended, especially for very obese patients and/or those with uncontrolled excessive weight gain. More frequent monitoring may be needed in the first few months of therapy and for those patients with known T2DM, dyslipidemia, or hepatic steatosis.
6. Hemoglobin and hematocrit may also be included in the routine monitoring for menstruating women.
7. As mentioned above, IGF-I levels should be monitored as a surrogate measure of GH adequacy. Whenever possible, physical activity, job performance, psychological status, and quality of life should be monitored. In selected patients, cardiology evaluations (echocardiogram, treadmill stress test) may be indicated.

Treatment of adult GH deficiency is presumably a lifelong necessity. However, there are no long-term, randomized, placebo-controlled studies of GH replacement in adults; therefore, clinical experience is an essential element for guiding therapy. Adult patients receiving GH therapy can be followed less frequently than children, perhaps at 4- to 6-month intervals.

Safety and Contraindications

There are no long-term, randomized, placebo-controlled studies of GH therapy in any population. Safety and efficacy monitoring of GH replacement therapy is based primarily on observational data from large post-marketing surveillance databases, which together contain tens of thousands of patient years of treatment experience. Post-marketing sub-studies regarding PWS

have been published [116–119]. Despite the intrinsic methodological limitations of such studies due to the absence of a comparison (control) arm, these databases indicate that GH replacement is safe and confers distinct clinical benefits when administered in appropriate doses. Nevertheless, healthcare professionals should be aware of potential adverse events during GH therapy.

As described in preceding sections, GH therapy during childhood may be associated with changes in physical features and body proportions (faces, hands, feet) due to bone growth and remodeling. In children with PWS, these changes generally lead to a "normalization" of body features and are not considered adverse effects. However, after epiphyseal closure, continued treatment at childhood dose levels can lead to a coarsening of features and bone overgrowth, as is observed in acromegaly. Therefore, it is important to monitor the response to GH during childhood and transition to adult dosage when long bone growth has ceased.

Scoliosis is a common, progressive condition in PWS, regardless of GH therapy. Therefore, all children and adults with PWS should have regular monitoring of back curvature and appropriate orthopedic monitoring and treatment. Progression of scoliosis may worsen during rapid growth, such as during a pubertal growth spurt or, theoretically, with childhood GH or gonadal steroid therapy. However, studies have not shown an independent effect of GH therapy on progression in PWS [32, 120–122]. Reports indicate that GH therapy may improve bone quality and efficacy of surgical treatment for scoliosis [123].

Slipped capital femoral epiphysis (SCFE) is a childhood condition in which the femoral epiphyseal plate is dislocated posteriorly, resulting in hip (and referred) pain and an abnormal gait. This condition is known to be associated with non-PWS obesity and may also be associated with hypopituitarism, hypothyroidism, and GH therapy. A survey study of 898 members of PWSA (USA) revealed only 1 case of SCFE among 565 respondents, suggesting a much lower than expected incidence [124]. However, since pain is a major presenting sign of SCFE and individuals with PWS are known to have an increased pain threshold, this could be an underestimate. Clinicians and other caretakers should be vigilant for abnormalities in gait that could signal a need for further evaluation.

GH deficiency is associated with decreased body water, and GH replacement therapy can be associated with acute retention of salt and water. In both children and adults, this can manifest as pseudotumor cerebri or idiopathic intracranial hypertension, which is associated with acute onset of headache, visual changes, gait disturbance, nausea, and dizziness. This condition is accompanied by papilledema and could lead to visual loss, although this complication would be unusual for GH-associated cases. Treatment involves cessation and/or lowering of the GH dose. Pseudotumor cerebri has been rarely reported during GH treatment of PWS [30]; the risk may be comparable to the observed risk of 1.6 cases per 1000 patient years in GH-deficient non-PWS children [125].

Another manifestation of GH-related salt and water retention is peripheral edema, which occurs almost exclusively in adult GH-treated patients. This complication is said to be the most common emergent complaint during GH replacement therapy in adults, and it was particularly frequent in early investigations when higher doses were administered. As with pseudotumor cerebri, treatment involves a lowering of the GH dose. Mild to moderate peripheral edema has been anecdotally observed in adults with PWS receiving GH therapy; however, the frequency of this adverse event has not been defined. Peripheral edema also was reported in 3 of 12 pediatric patients with PWS who received higher-dose GH therapy [67].

In GH therapy of non-PWS, pituitary GH deficiency often unmasks an underlying TSH deficiency, leading to deficiencies in T4 (thyroxine) and T3 (triiodothyronine). Therefore, measurement of thyroid hormone levels (T4, T3, and/or the free forms of these hormones) is recommended for true pituitary GH deficiency. However, this co-occurrence of GH and TSH deficiency has not been reported in PWS. In addition, studies have not shown an increased risk for

hypothyroidism, either central (TSH deficiency) or peripheral (primary hypothyroidism) in PWS.

GH therapy can cause a decreased T4 level by increasing the conversion of T4 to T3; in these cases, T4 may be low or low to normal, while TSH and T3 will be normal [64]. Increased T3 levels within the normal range, with normal T4 and TSH levels, were observed in a randomized, controlled trial of GH treatment of adults with PWS [26]. Thyroid function, as assessed by thyrotropin-releasing hormone stimulation test, did not change during 1–2 years of GH treatment in children with PWS [126].

GH therapy can acutely decrease insulin sensitivity by counteracting endogenous insulin action. In cases where there is obesity preceding insulin resistance, and/or a genetic predisposition to insulin resistance, the addition of GH therapy can trigger the onset of T2DM. Furthermore, GH therapy could potentially worsen glycemic control in patients with poorly controlled T2DM, although the longer-term effects on lean and fat mass may increase insulin sensitivity. Post-marketing surveillance databases indicate that this type of complication may be particularly frequent in GH-treated patients with Turner syndrome or intracranial tumors [64]. Increased frequency of GH-induced T2DM has not been formally reported in PWS. GH therapy does not adversely affect carbohydrate metabolism in children with PWS who do not have preceding evidence for insulin resistance and/or glucose intolerance [127, 128].

Ongoing analyses of post-marketing surveillance databases have not shown an increased risk for primary, secondary, or recurrent cancers in GH-treated individuals, including those with PWS [64, 129].

In 2002, Eiholzer and colleagues reported two cases of sudden death in children with PWS during GH treatment [130, 131]. These cases and subsequent published reports [132, 133] raised an international concern that GH therapy may increase mortality risk in children with PWS. A worldwide survey of GH-treated PWS patients through mid-2004 revealed a total of 13 cases of death in children, aged 0.7–16 years, treated for 2 weeks to 1.5 years. Although the cause of death was not definitely determined in all cases, respiratory compromise, often with concurrent pulmonary infection, seems to be a common link [133].

These cases spurred a worldwide interest in mortality in PWS. Published reports indicate that over the same approximate time period, there have been more than 30 deaths in children with PWS who were *not* treated with GH [130–132, 134–138], and the authors are aware of additional unpublished cases. The cases with known cause of death are remarkably similar to those reported during GH therapy. No relationship to GH treatment was found in a review of 104 deaths over 11 years recorded in the French Reference Center for PWS [139].

Additional arguments against a relationship of GH therapy and risk of sudden death include the absence of evidence for GH as a cause for increased morbidity that could contribute to mortality in PWS and studies showing that GH therapy improves respiratory function in PWS [74, 75]. Moreover, the dose of GH is known for 11 of the 13 cases of death during GH therapy and all were relatively low, with only 2 individuals treated at or above the recommended level (0.24 and 0.26 mg/kg/week) and the remainder treated at 0.10–0.23 mg/kg/week [140]. A logical conclusion based on current information might be that which was suggested by a statement in the first published report [131]: "The boy reported here . . . thus died before the effects of GH therapy could manifest themselves . . ."

Finally, there have been anecdotal concerns that GH therapy could exacerbate behavioral problems in children with PWS. However, as mentioned previously, GH treatment has been associated with behavioral improvement [77]. Detailed, objective behavioral studies conducted during a 2-year, controlled study of GH therapy in 41 children (27 treatment, 14 control) found no differences for measures of attentional symptoms, anxiety, obsessive-compulsive complex, violence, or psychotic symptoms [79].

In summary, GH therapy in general has had a remarkable safety record. Adverse effects specifically observed in PWS are either reversible with cessation or reduction of GH therapy (water and salt retention, exacerbation of insulin resistance) or related to preexisting conditions that require

separate attention (scoliosis). Caretakers should be vigilant for the possibility of rare events, such as malignancy, and for complications that are usually signaled by pain in non-PWS conditions (SCFE, pseudotumor cerebri), although none of these complications have been reported to be specifically associated with GH treatment of PWS. Current concerns about the risk for sudden death in PWS are under investigation, and a relationship to GH therapy is not supported by available data.

Comprehensive Care

Traditional care guidelines for individuals with PWS, including many of those included in this text, are based on experience in non-GH-treated individuals. At the risk of oversimplifying, the major guidelines can be summarized as follows:

1. Strict dietary limitations to prevent overweight
2. Developmental, occupational, and educational therapy
3. Intensive physical therapy and exercise to counteract the hypotonia
4. Psychological/psychiatric evaluation and therapy

Although the above therapies have provided immeasurable benefits for countless individuals with PWS and their caretakers, they produce no substantial changes in the characteristic body habitus, limited muscle mass and function, or behavior. At each stage of life, a typical, distinctive "look" could be expected, as clearly depicted in the life-sequence pictures of non-GH-treated individuals included in this book and other references [73].

As is also depicted in life-sequence photographs in this text and elsewhere, GH therapy has resulted in a remarkable change in the appearance and physical function of individuals with PWS, alleviating many but not all of the associated morbidities as summarized in Table 7.1 [34]. These changes are most dramatic for individuals treated with GH from a young age but may also be important for adolescents and adults.

For many of the morbidities, the full therapeutic effects of GH are not yet completely defined. GH may have a dual effect on the spectrum of disorders related to obesity, an acute exacerbation of insulin resistance, followed by increased insulin sensitivity as muscle mass increases; this possibility is currently under investigation. Although initial data indicate potential beneficial effects on psychosocial and behavioral function,

Table 7.1 Morbidity and treatment in Prader-Willi syndrome

Morbidity	Contributory factors	Therapy
Genital hypoplasia, cryptorchidism, hypogonadism	Gonadotropin deficiency	Surgery, gonadal steroids
Hypotonia	GH/IGF deficiency, other factors not yet defined	Physical therapy, GH
Scoliosis	Hypotonia	Orthopedic care
Osteoporosis	GH/IGF deficiency, hypogonadism	GH, gonadal steroids, bisphosphonates
Respiratory dysfunction	Hypotonia, possible central component	GH, surgery, and supportive care if clinically indicated
Obesity (increased body fat, independent of weight)	Not fully defined	Diet, exercise, GH
Hyperphagia, overweight	Not fully defined	Diet, exercise, GH
Acromicria	GH/IGF deficiency	GH
Short stature	GH/IGF deficiency	GH
Insulin resistance, T2DM, related conditions	Obesity	Diet, exercise, GH effect
Cognitive defect	Not fully defined	Behavioral and educational therapy
OCD-like behavior, psychosis	Not fully defined	Psychotherapy ± psychotropic agents
Low academic and social functioning	Composite effect of physical and mental limitations	Behavioral, educational, and psychotherapy, possible GH effect

long-term treatment outcomes have not been reported.

The improvements in physical appearance and function inevitably facilitate psychosocial integration and interactions. In addition, there may be increased resting and active energy expenditure related to increased muscle mass. Additionally, improved medical attention to gonadal steroid replacement may further enhance physical appearance and function. The implications of these changes for comprehensive care of PWS are not completely known and are likely to be fully defined only with long-term follow-up of patients receiving GH and gonadal steroid replacement. However, a comprehensive team approach to the individual with PWS is the most logical avenue for provision of optimal care (see Chap. 25).

We end this chapter with a few of the additional medical care considerations that are introduced by hormone replacement recommendations:

- *Diet:* It is not clear at this time whether GH has a significant effect on hyperphagia, although experience suggests that dietary control remains a crucial element of care. However, calorie-guided diets must now take into account the increased requirements associated with GH therapy. Strict application of traditional PWS calorie limitations may lead to undernutrition. Weight, body composition, and, for children, growth should be carefully monitored.
- *Physical therapy and exercise:* Traditional expectations for improvement need to be raised, and therapy should be individualized. For school-age children, mainstreaming into usual age-related physical education and selected other activities may be possible.
- *Cognitive function and behavior:* There are no conclusive scientific evidence that GH therapy improves cognitive abilities or behavior, although parents have anecdotally reported improvements in memory and school performance. Therapists and educators should be aware that adherence to traditional assumptions of cognitive limitations may not be appropriate. On the other hand, normalization of physical appearance does not eliminate the need for proper attention to typical PWS-related behavior disorders.
- *Sexual behavior:* Normalization of physical function and appearance increases the likelihood of social interactions that may result in sexual activity and relationships. Age-appropriate counseling, caretaker education, birth control precautions, and minimization of risks for sexual abuse and sexually transmitted disease are important elements of a comprehensive team approach.

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Part III

Multidisciplinary Management of Prader-Willi Syndrome

8 Neurodevelopmental and Neuropsychological Aspects of Prader-Willi Syndrome

Barbara Y. Whitman and Jennifer L. Heithaus

Introduction

The neurodevelopmental profile of Prader-Willi syndrome (PWS) continues to unfold with a patterned complexity across the life span. The neurodevelopmental profile of individuals with PWS, also referred to as the behavior phenotype, has predictable groupings of behaviors that present as distinct clinical patterns over the lifespan. While the most distinctive and notable features are food-related behaviors, PWS presents with specific yet varied features in three other general categories: (1) the neurocognitive profile (i.e., intelligence, language, learning profile), (2) behaviors related to social interaction and communication, and (3) mental health symptoms and diagnoses. Distinct changes occur in each area throughout the lifespan, and environmental influences further alter behavioral trajectories and can produce variations in an individual over time. Further, genetic subtypes (chromosome 15 deletion versus uniparental disomy [UPD]) are a demonstrated source of variability, further adding to the complexity. Some of this reported variability is reflected in studies that predate both consensus diagnostic criteria (1993) [1] and comprehensive confirmatory genetic technology (mid- to late 1990s, M.G. Butler, personal communication). Thus, some of the earlier reported differences may also result from different ascertainment, diagnostic strategies, and varied population characteristics [2–4].

Collectively, studies document that hyperphagia, skin picking, stubbornness, temper tantrums, and diagnosable psychopathology (both internalizing and externalizing behaviors) are common to most affected individuals [5, 6], yet substantial variation is observed even among these common characteristics. And, while advances in understanding the impact of genetic variations and environmental influences on the expression of this behavioral profile have been made, our understanding of these aspects of the syndrome remains rudimentary and imperfect—a state of affairs that frustrates parents and caregivers alike.

In this chapter, we will summarize the current understandings of the neurodevelopmental/behavioral aspects of PWS as they present clinically in the specific epochs of development in individuals with PWS: infancy and young childhood (ages 0–4), mid-childhood, adolescence, and adulthood. It is first necessary, however, to revisit the historical and methodological factors that influence the status of research in this area. These include diagnostic/genetic issues, an underappreciation of the pervasiveness of central nervous system involvement, inadequate cogni-

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tive and behavior measurement tools, and a strong bias toward measuring problematic behaviors. Behavioral variability, with limitations set by historical responses and biased measurement of neurodevelopment and behavior, has impaired optimal approaches to support individuals with PWS and has led to medication use with variable and often limited benefit, especially for individuals UPD [7].

Diagnostic/Genetic Issues Consensus diagnostic criteria and confirmatory genetic testing for PWS have been readily available for only a fraction of the history of the diagnosis. For those with a deletion, genetically confirmed early diagnosis became possible in the early 1980s when high-resolution chromosome techniques became available in most cytogenetic laboratories. These techniques, however, both required extensive experience to avoid false positive and false negative reporting and were insensitive to those with uniparental disomy. Full, reliable, and valid laboratory confirmation was not certain until methylation PCR became readily available to most genetic testing laboratories in the mid- to late 1990s (M.G. Butler, personal communication). Prior to that, diagnosis was often suspected but delayed until the emergence of the abnormal eating constellation and obesity. For those with a deletion, the average age at diagnosis was 6 years, and for those with uniparental disomy, age 9 [8]. Even in the year 2021, a small but significant number of youngsters appear to meet most diagnostic criteria and match the behavioral profile for Prader-Willi syndrome yet fail diagnostic confirmation by genetic testing. Earlier study populations that had neither the benefit of standardized criteria nor genetic confirmation likely included some persons who did not have PWS; the influence of these individuals on the data is indeterminable at this point. Further, even among those with PWS, study participation may have been biased toward those with the most intense or severe behaviors.

Thus, while behavior studies prior to the early 1990s can be helpful, later studies of behavior that include only those with genetic confirmation of PWS must be given greater weight. Studies including reliable categorization of genetic subtype (BP1 and BP2 deletion, uniparental disomy [UPD], or imprinting center defect) are still relatively recent but increasingly common and help elucidate the differential impact of genetic subtype on behavioral outcomes.

Underappreciation of the Pervasiveness of Central Nervous System Involvement What makes PWS unique as a genetic diagnosis is the range of developmental differences, mental health diagnoses, and behavioral features associated with the diagnosis. However, because of the constellation of metabolic abnormalities associated with PWS, the (hypothesized) central etiologic role of hypothalamic dysfunction is frequently emphasized, often to the minimization of other brain mechanisms. Recent studies are limited but have expanded upon underlying structural differences in the central nervous system and have shown frank differences. Of note, one study of 12 individuals with PWS showed decreased gray-matter volume in the orbitofrontal cortex, caudate nucleus, inferior temporal gyrus, precentral gyrus, supplementary motor area, postcentral gyrus, and cerebellum [9]. The typical pattern of cognitive and learning deficits associated with PWS supports that PWS is a pervasive (affecting many areas of the brain) neurodevelopmental disorder. Four separate sources of cognitive deficits have been identified: (1) depressed general cognitive functioning or IQ [10], (2) general processing deficits including short-term memory [11], (3) language processing deficits [12, 13], and (4) an inability to meld diverse and detailed internal information into relevant higher-order abstract and metacognitive concepts that guide behavior over the long term [14, 15]. Each of these deficits implies the involvement of multiple neural systems, beyond that predicted from hypothalamic dysfunction alone. Additionally, affected individuals display an evolving, multistage behavioral picture that differs somewhat between those with a deletion and those with uniparental disomy. Clearly the neurodevelopmental/neurocognitive picture associated with PWS reflects the dysfunction of a

distributed brain system, the complexities of which have yet to be fully described.

The conceptual framework used to approach these features is also varied in the literature [16]. Traditionally, a DSM-V and/or medical diagnosis has been assigned to those that have met diagnostic criteria. With the increasing popularity of applied behavioral analysis as a response to challenging behavior, some classify psychopathology as behavior problems instead of distinct diagnoses. Most recently, approaching problems using the research domain criteria (RDC) connect psychopathology to disturbances in brain networks and mechanisms so as to identify underlying pathophysiology and provide the best targeted treatment [16]. In order to provide a holistic approach, all three viewpoints are included in this chapter.

Table 8.1 Patterns of age-related feeding behaviors in Prader-Willi syndrome

Age	Behavior
Early Infancy, often through 9 months	Feeding difficulty and disinterest, poor suck, minimal appetite, failure to thrive
Late infancy (9–25 mos)	Resolution of feeding difficulties with typical feeding behaviors (with improved growth)
Toddlerhood (2–4.5 yrs)	Relatively steady feeding behaviors (with increasing weight)
Young childhood (4.5–8 yrs)	Increased appetite, definite food obsessions, and preoccupations (with increasing weight)
Childhood to adulthood (8 yrs+)	Hyperphagia, inability to reach satiety, continued food obsessions, and preoccupations
Adulthood	Improved satiety and appetite (note: *many* individuals do not reach this phase)

Adapted from Miller et al. (2011) and McAllister, Whittington, & Holland (2011)

General Factors Influencing Neurodevelopment and Behavior

Food-Related Behaviors Food-related behaviors remain the primary defining syndromic feature for most family, health, and other care providers. When poorly or improperly managed, hyperphagia, along with the resulting obesity and associated negative behavior, is usually the central difficulty for which families seek help. However, hyperphagia is only one of many behaviors in the food-related behavioral constellation which also includes preoccupations surrounding food; food-seeking/foraging; sneaking, hiding, and hoarding; eating unusual or noxious food-related items (sticks of butter, used cooking grease, dog food, decaying or rotten food, food-flavored items such as shampoos, etc.); and for many, manipulative and occasionally illegal behaviors in an effort to obtain food.

Underlying food-related desires change over time across the lifespan in a gradual, yet predictable, pattern, and are summarized in Table 8.1. It is critical to note that two separate studies, one with 46 children under the age of 5 years and another with 79 participants over the lifespan, demonstrated that the transition from limited desire to eat to hyperphagia is gradual and is *preceded* by obesity [17–20]. Understanding overall patterns in eating-related behavior provides context for interpreting specific behaviors and providing appropriate responses, which is discussed in detail below and in Chap. 12.

Etiology of the Abnormal Food-Related Constellation Despite seven decades of research, the underlying physiologic abnormalities behind the hyperphagia remain unspecified. The mechanism of disordered eating in PWS currently proposed is based on multiple, interrelated models, centrally focused on abnormal satiety as the primary driver, as opposed to hunger [18]. Models also include an elevated sense of food as a reward in neuronal pathways, abnormalities of the hypothalamus in feeding regulation for food [18, 21–24], and prenatal genetic upregulation of pathways for energy balance and satiation [18]. This is a far more complex etiology than historically described [25–27], including a theoretical reorientation that views PWS as a *starvation syndrome* rather than an obesity syndrome [18, 28]. In this view, the obesity of PWS is seen as resulting from a physiologic signaling defect indicating that the body is in a constant state of starvation, similar to that of malnourished youngsters [29].

Central motivation of the increased food drive is further influenced by the abnormal reward response that an individual with PWS has with food. In a study evaluating the functional MRIs of 14 individuals with PWS with matched controls with and without obesity, when seeing food-related stimuli prior to meals, those with PWS had increased activity in reward/limbic regions (nucleus accumbens, amygdala) and decreased activity in the hypothalamus and hippocampus. Post meal, those with PWS exhibited higher subcortical activation (hypothalamus, amygdala, hippocampus) and decreased cortical activation (dorsolateral prefrontal cortex and orbitofrontal cortex) compared to matched controls with obesity [30]. This pattern suggests that there is hyperactivation in subcortical reward circuitry and hypoactivation in cortical inhibitory regions after eating in PWS [30].

While interpreting the complex biological mechanisms is beyond the scope of this chapter, viewing PWS as a starvation syndrome suggests a basis for explaining the failure of the food-related behaviors to respond to anorexigenic or obesity medications. In the absence of adjunctive medications, treatment remains primarily behavioral and preventive. Strategies for preventing and coping with this behavior vary according to individual characteristics and family needs [31].

Hyperphagia, Food Seeking, and Hoarding Behaviors Hyperphagia is not unique to PWS; several syndromes and conditions include some degree of hyperphagia (e.g., fragile X syndrome, Kleine-Levin syndrome, WAGR syndrome, and "normal" obesity). Nonetheless clear differences distinguish the eating patterns associated with PWS from those of other conditions. Foremost among these is the age-related emergence, escalation, and intensification of hyperphagia following several years of normal to poor eating and often failure to thrive [18, 20, 32]. Further distinguishing characteristics include duration of eating, amount of food eaten, and a delayed to absent deceleration of eating when satiety should be apparent.

Several studies have compared the *duration and quantity of eating* of those with PWS with that of control subjects (either obese of non-syndromic origin, normal weight, or other genetically disordered individuals) [22, 33, 34]. Common to all studies was full access to food by all subjects for a full hour. In all studies, those with PWS, except for the very youngest participants, continued to eat throughout the hour, while control subjects stopped eating within 15 to 20 minutes. For most nonaffected individuals, a deceleration of eating is observed prior to complete eating cessation; however, there was no clear indication that those with PWS would have totally ceased eating had food continued to be made available.

Noting the tendency toward slightly longer pauses near the end of the study hour, several follow-up studies used a similar methodology with the exception that when the participants with PWS appeared to be finished, they were asked to leave the room [35, 36]. With this slight modification, all participants with PWS finished eating in 45 minutes. This was still substantially longer than control subjects, who, as before, completed eating in 15 to 20 minutes. In addition to an extended duration of eating compared with control participants, those with Prader-Willi syndrome consumed far greater quantities of food than nonaffected controls. Several authors reported that even when those with PWS appeared sated and stopped eating, the satiety was short lived and food seeking resumed far more rapidly than in an unaffected population [22].

The failure of intake regulation is also reflected in studies designed to look at *food choices* of persons with Prader-Willi syndrome, particularly those that look at a choice between a larger quantity of food versus a smaller quantity but more desirable food [37–39]. One study offered a choice between immediate access to a small amount of a previously determined favorite food of the participant and a larger amount of a less-preferred food following a brief time delay [40]. Seven persons with PWS and six matched obese persons participated. In all instances, those with

PWS opted for the delay followed by the larger quantity, while the control group was equally likely to select the smaller amount of more-desired food as to delay for quantity. A similarly designed, larger follow-up study offered an immediate but small amount of a desired food versus a delay followed by a larger amount of the same food. Similar results were obtained. Two separate studies demonstrate underlying pathophysiological changes consistent with food quantity being the central value over food choice. In a study evaluating positron emission topography in 18 individuals with PWS, activation of the amygdala and medial orbitofrontal cortex was not associated with highly valued foods [41], and in a study of fMRI in 9 individuals with PWS, there was greater activation in the orbitofrontal cortex, medial prefrontal cortex, insula, hippocampus, and parahippocampal gyrus to food pictures post-meal compared to pre-meal [42]. Both of these findings are the opposite of what is seen with food motivation in nonobese neurotypical individuals.

Water consumption is unique compared to intake of food and drink of nonaffected individuals. A study following 47 individuals showed that over 75% of infants avoided water without flavoring and had a small daily intake of water [43]. The majority of these individuals had similar water intake through adulthood; however, a small group (15%) has excessive water intake later in life, to the point that two individuals had hyponatremia in combination with psychiatric medication use.

That *food seeking* is prevalent among those with PWS is not surprising given these results, and indeed at least 50% of those affected actively seek food [44] including foraging for food and food stealing [45, 46]. Food seeking typically occurs covertly. Clinical data and anecdotal reports are rife with stories of food-seeking incidents by affected individuals and the impact of these behaviors on obesity management, family stress, and the ultimate adjustment of both the affected individual and his/her family [5, 47, 48]. For some, food seeking is opportunistic; that is, if food is accessible and usual caretakers are absent or otherwise preoccupied (e.g., parent talking with a friend), the affected individual seizes the opportunity, often hiding the prize (usually in clothes) for later consumption. Others are more active in *making* opportunities, such as "borrowing" money from a parent's wallet for later food purchase, or asking to use the school restroom and while en route "checking out the desk" of a teacher known to keep candy in a desk drawer. At the most severe end, many look for every opportunity to escape the confines of a caregiver so they can seek food, be it from neighbors, local groceries, or any other source of abundant food.

The severity of food-related behaviors cannot be underestimated. A considerable number of individuals with PWS across the age spectrum die directly due to catastrophic eating-related behaviors, such as stomach rupture and choking. This is independent of the many individuals that die from medical complications of obesity. A 2017 study evaluating direct cause of death for those with PWS noted that 10% of individual died from gastrointestinal problems (i.e., perforation, distension, or obstruction), and many individuals died from risk-taking behaviors, likely related to food and food access, such as choking (6%) and accidents (6%) [49]. In children under 18 years, half of deaths were related (directly or indirectly) to choking and accidents.

In addition to extraordinary food-seeking and eating behaviors, even ordinary conversation reflects a constant preoccupation with food. Clinical descriptions indicate a constant need to know when the next food will be available, what that food might be, how much will be served, how it will be cooked, and an assurance that the information provided is certain. In the larger environment, food or restaurant advertisements, newspaper and magazine pictures and recipes, and other visual reminders of food frequently become the subject of discussion and "collections." And jigsaw puzzles, a favorite pastime of many persons with PWS, become even more enjoyable when the subject of the puzzle is food related.

Neurocognitive Profile

Inadequate Cognitive and Behavior Measurement Tools Tools that measure cognition and behavior are frequently imprecise and focus on only a small segment of behavior. For instance, many IQ tests fail both to detect and to account for speech and language deficits. And while speech and language deficits can be separately tested, the interplay between speech and language deficits and uneven cognitive abilities is more difficult to demonstrate. Additionally, many earlier studies failed to use standardized behavioral measures or used measures standardized on cognitively normal populations. The uncritical application of measures standardized in normal or non-PWS populations may inaccurately describe and overestimate the severity of behaviors noted in affected individuals. Further, some researchers measure the occurrence of specific behaviors [50, 51], whereas others use measures that summarize several behaviors into more abstract conceptual groupings (e.g., the internalizing/externalizing factors of the Child Behavior Scale by Achenbach [3, 52]) and personality traits (e.g., California Child Q Set [53, 54]), the relevance of which for a PWS population has yet to be established.

An additional measurement problem is found in the amount of quality testing in well-designed studies. Both children and adults with PWS can be particularly difficult to test. Shortened attention spans and reduced tolerance for things that are difficult for the individual, combined with expressive language difficulties and, for many, slower-than-average processing speeds, frequently lead to behavioral refusals to complete testing protocols.

Early Childhood: Global Developmental Delay One of the earliest neurodevelopmental concerns in PWS is global developmental delay, which is noted starting in infancy. Decreased fetal movement often precedes this significant developmental delay [55]. Delay in motor and language skills can be noted within the first few weeks and are definite by 6 months [56]. Children with PWS show significant motor delay as part of their manifestation of global delay, and often begin to walk between 24 and 30 months, though timing of skill development is highly variable [57]. Treatment with growth hormone in PWS is commonly initiated in early childhood and may positively alter the natural developmental trajectory of PWS: studies have shown that children treated early with growth hormone have a trend toward improved motor development and mobility [58]. However, wide variability is seen in those treated and untreated with growth hormone, and motor delay is still significant in all. Language milestones are delayed as well, with first word often at 17–23 months, though again, significant variation is seen from individual to individual [57]. Treatment with growth hormone may significantly improve language and cognitive development, with a study showing first word was spoken at 14 months in 12 treated young children [58]. This early presentation of delay is in combination with decreased sensory responses (especially to pain), physical inactivity, food-seeking behaviors, skin picking, and developing speech articulation problems, all of which are often present by 2 years of age [57].

Communication milestones are also altered early in development and may precede autism-related behaviors. The use of the developmental screening tool the Ages and Stages Questionnaire, 3rd edition (ASQ-3), has shown nearly 80% of children under 3 years old with PWS screen with high-risk concern (defined as either “monitor” or “fail” scores) in communication delay [59]. The study reporting this finding also noted that 84% of participants above the age of 3 screened at high risk for autism spectrum disorder, defined as a t-score >70 on the Gilliam Autism Rating Scale, Third Edition (GARS-3).

Middle Childhood: Cognitive Ability Including Intellectual Disability Decreased intellectual functioning, presumably in the form of what was then termed mental retardation, was among the four original defining characteristics of PWS [36, 60, 61]. Those studies [4, 8, 62–66] in which individual test results or ranges have been reported document a

wide range of intellectual abilities, with overall IQ scores ranging from 12 to 100. Curfs's and Fryns's [67] oft-quoted summary of 57 studies including 575 individuals of unspecified ages from a number of countries yielded the following distribution of IQ scores: normal 4.9%, borderline 27.8%, mild mental retardation 34.4%, moderate mental retardation 27.3%, severe to profound retardation 5.6%. However, methodologic concerns render these figures questionable: the included studies varied from case reports to large surveys; few of the study populations were genetically confirmed, raising the likelihood that the studies included those who did not have PWS. And few authors reported the basis for determining "mental retardation," including IQ thresholds for intellectual disability. Further, many studies failed to include measures of adaptive behavior, relying solely on IQ scores to determine the presence of an intellectual disability, thus failing dual criteria requirements.

Over time, studies have shifted to using a broader range of IQ test (e.g., the Wechsler series) which provides different IQ results than those using a more narrowly focused, verbally based instrument (e.g., earlier versions of the Stanford-Binet) that emphasizes verbal abilities more heavily than non-verbal abilities. While testing standardization has improved somewhat over time, nonetheless, limitations in testing the abilities of individuals remains. Some studies administer a subset of the test protocol and prorate overall scores from that subset, and some studies modify administration protocols (e.g. spreading the testing over several days) thus limiting the overall value of the findings and limiting the ability to generalize across the PWS population.

A valid determination of cognitive ranges requires (1) genetic confirmation of the diagnosis, (2) directly and validly administered, age-appropriate standardized testing, and (3) measures of adaptive behavior. Five studies that meet the majority of these criteria are summarized in Table 8.2. The Gross-Tsur et al. data [68] are remarkable for the large percentage of children testing in the normal range. The authors reported that this sample of 18 represents 86% of the total number of individuals with Prader-Willi syndrome known in Israel at the time of study. Clearly this population has a distribution of IQ scores that is quite different from the remaining four studies. Averaging across the four remaining studies, all with approximately the same number of participants, 25.5% have IQ scores above 70, 43% score in the range of mild intellectual disability, 27.7% in the region of intellectual disability, and 3.8% in the severe to profound range. When compared with Curfs's and Fryns's 1992 estimates [67], this combined sample of 203 subjects yields substantially fewer who score in the Borderline to Normal range (32.7% versus 25.5%) and a substantially greater portion scoring in the category of Mild Intellectual Disability (see Table 8.3). Recall, however, that these are cognitive scores only and do not take into

Table 8.2 Studies of IQ in individuals with Prader-Willi syndrome

			Percent of subjects testing in each IQ range					
Study	*N*	Avg. age	Normal		Borderline	Mild ID	Mod. ID	Severe/profound
Einfeld et al. [5]	46	17.7[a]		21.6*		64.9	13.5	0.0
Gross-Tsur et al. [68]	18	14.3[b]	17.0	(73.0)*	56.0	27.0	0.0	0.0
Descheemaeker et al. [69]	55	14.1[c]	9.0	(25.4)*	16.4	27.3	40.0	7.3
Whittington et al. [70]	55	21.0[d]	5.5	(31.0)*	25.5	41.8	27.2	0.0
				IQ ≥ 70		60–69	50–59	≤49
Roof et al. [71]	47	23.2[e]		24.0*		38.0	30.0	8.0

*Subjects testing at normal or borderline; the numbers in parentheses are sums of the normal and borderline subjects in those studies, provided for comparison purposes with the Einfeld et al. and Roof et al. data

[a]Age range: NA. Only half of subjects genetically confirmed; most IQs from records (S.L. Einfeld, personal communication, 2004)

[b]Age range: 8.3–23.5 yrs. Did not give a measure of adaptive functioning

[c]Age range: 1–49 yrs. (A. Vogels, personal communication, 2004)

[d]Age range: 5–46 yrs

[e]Age range: 10–55 yrs

Table 8.3 Estimates of IQ in Prader-Willi syndrome based on multiple studies

			Percent of subjects testing in each range			
Survey	*N*	Normal	Borderline	Mild MR	Mod. MR	Severe/profound
Curfs and Fryns [67][a]	575	32.7		34.4	27.3	5.6
Author[b]	203	25.5		43.0	27.7	3.8

[a] Summary of 57 studies; subjects' ages unspecified
[b] Averages of data from four recent studies shown in Table 8.1, excluding data from Gross-Tsur et al. [68]

account adaptive behavior profiles; thus, these figures are only approximate, with the true percentages in the borderline range expected to be somewhat lower while those in the mild intellectual disabled range would be somewhat higher.

At least one group of authors [70] suggests that the distribution of scores approximates the normal curve usually associated with IQ scores, but with the overall mean shifted downward 30–40 points. They attribute this to a "direct and specific effect on brain development because of the absence of expression of an imprinted gene that is part of the PWS genotype" [70]. This explanation, however, cannot account for the very different distribution underlying the Israeli data. Evaluating intelligence in the context of genetic predisposition of the family shows persistent deficits in those with PWS and also suggests metabolic changes in the central nervous system as related pathophysiology. In a study with 17 participants with PWS (10 with deletion subtype and 7 with maternal UPD), 18 unrelated controls with non-syndromic early-onset obesity, and 21 siblings of those with PWS or early-onset obesity, those with PWS had a mean general intellectual ability of 63.3 and sibling control subjects had a mean of 106.4 on testing via the Woodcock-Johnson Test of Cognitive Ability and Academic Achievement, Third Edition [19]. This difference in IQ is of the magnitude suggested by preceding studies. Also of note, functional MRI showed white matter lesions in 6 subjects with PWS and 5 with early-onset obesity, and none in matched sibling controls. The authors speculate that altered levels of adipokines, insulin, or neuropeptide-Y possibly alter the brain structure and function prior to the completion of myelination as a possible underlying mechanism, though this remains speculation only [19]. In looking at the correlation of IQ of individuals with PWS to their siblings, overall correlation was 0.3, though correlation of those with the deletion compared to their siblings, and typical siblings compared to typical siblings was 0.5, and correlation of those with UPD to their siblings was −0.07 [72]. This study was limited by size (33 participants with 38 siblings in total), though direct measurement of all individuals through the Weschler Intelligence Scales was included.

Recent emphasis on understanding cognition is framed by genetic subtypes, and patterns of intelligence in the context of genetic subtypes are emerging. Data on variation of patterns of intelligence is varied across studies, and studies in general are limited by sheer number and also by limitations as described above. A summary of available studies evaluating intelligence quotient by genetic subtype is given in Table 8.4. Data showing differences in performance based on deletion breakpoints has been demonstrated in multiple studies, with BP1 performing worse than BP2 across multiple domains. Of note, growth hormone treatment status is not described by the studies included below, which is a factor that may significantly alter results.

Some studies have reported that those with UPD may have higher verbal IQ scores and those with a deletion may have higher performance/nonverbal IQ scores [73] and better performance on some non-verbal tasks on varied testing modalities (e.g., object assembly and digit symbol coding tasks) [74]. One study noted that those individuals with deletions at BP1 were associated with higher verbal performance by nearly 20 performance points than what was seen in those with deletions at BP2 [73]. Overall, based on small (often under 10 performance points) and inconsistent degree of variation found between subtypes, it is unclear if this variation in itself leads to any measurable difference in outcomes; thus, this data should be considered rudimentary.

Table 8.4 Estimates of IQ in Prader-Willi syndrome by genetic subtype based on multiple studies

	Average full scale IQ scores (n)				
Study	All deletion type	Deletion, BP1	Deletion, BP2	Maternal Uniparental Disomy	Testing modalities
Whittington et al. [72]	66.9 (23)	57.8 (4)	70.7 (12)	71.4 (10)	Wechsler Intelligence Scales (age appropriate versions)
Milner et al. [73]	70.8 (45)	64.7 (13)	73.2 (31)	69.5 (47)	Wechsler Adult Intelligence Scale, Revised (WAIS-R), Wechsler Abbreviated Scale of Intelligence, Mullen Scales of Early Learning (all preferred), Raven's Standard Progressive Matrices, or Raven's Coloured Progressive Matrices
Copet et al. [74][a]	52 (52)	–	–	51 (20)	Wechsler Adult Intelligence Scale III

[a]Authors attribute relatively worsened scores in comparison to other studies due to potential sampling bias; participants for this study were in a French inpatient unit for those that have had significant difficulty living in group homes

Analyzing the results further, children with UPD have lower baseline scores than children with the deletion subtype; however, children with UPD showed a greater improvement on the block design test.

Adolescence and Adulthood: Stability of Cognitive Functioning In addition to the overall levels of cognitive ability, several additional aspects of cognitive functioning have been investigated. Early cross-sectional reports suggested that IQ scores in PWS decline with age [60, 62, 75]. Early data from Vogels [76] demonstrated differences in IQ in those over (IQ = 57.2) and under age 12 (IQ = 63.8): a trend toward a significant reduction ($p = 0.09$) in IQ scores is noted for the older group. Subsequent studies failed to support a decline in IQ scores over time [64, 77], leading to the conclusion that, in contrast to other genetic disorders (e.g., fragile X and Down syndromes), the cognitive trajectories of those with PWS appear to be stable over time. However, a decline in adaptive function has been noted in older individuals with PWS; it is unclear how this is related to cognitive decline [78]. Full clarification of this issue requires longitudinal studies of several cohorts of affected individuals and is beyond the scope of current knowledge.

Treatment with growth hormone has shown benefits in maintaining cognition [79, 80]. In a 2012 study by Siemensma et al. [80], 50 prepubertal children aged 3.5 to 14 years were followed for 4 years in a randomized control trial. Cognition was measured every 6 months via four subtests on age-appropriate Wechsler Intelligence Scales. Children undergoing growth hormone treatment maintained baseline scores; however, children who did not receive treatment showed decline on subtests in similarities and vocabulary. Those who received growth hormone additionally had a small but consistently improved performance in abstract reasoning and visuospatial skills, with significantly higher scores in similarities and block design tests. Overall improvement for all participants was enhanced in children who were of a younger chronological age at initiation of treatment. A separate study by Dykens et al. [79] further supports these findings. The authors studied a cohort of 173 individuals with PWS of ages 4–21 years, of whom 43 were treatment naïve and 130 received growth hormone treatment. The study demonstrated that participants who received growth hormone had significantly higher verbal and composite IQs on testing with the Kaufman Brief Intelligence test, 2nd edition (KBIT-2), with a gross mean difference magnitude of nearly a standard deviation. While individuals in the treatment group had a wide range of cognitive skills, early initiation of growth hormone treatment (by 12 months of age) was associated with higher nonverbal and composite IQs than those that initiated treatment at 1–5 yrs of age. Treatment groups separated by age of initiation showed stable IQ scores over time across all groups, again suggesting that growth hormone maintains cognition.

Evidence that treatment with growth hormone maintains or improves cognition further complicates data acquisition and interpretation about the natural progression of the neurocognitive aspects of the disorder, given it is a standard of care and a highly utilized treatment.

Academic Underachievement It is generally accepted that across the cognitive spectrum, academic performance is substantially below that predicted by composite (full scale) IQ scores, although exceptions are noted [11, 55, 64, 71, 81]. Part of this discrepancy may be a computational artifact associated with the calculation of full scale, verbal, and performance IQ. When test protocols are closely examined, most affected individuals demonstrate wide individual variability among the subtest scores comprising verbal, performance, and overall full scale IQs (subtest scatter). This uneven pattern of cognitive abilities is similar to that seen in children with learning disabilities [68, 82]. When significant subtest variability exists, composite verbal, performance, and full scale IQ scores are unreliable and frequently inaccurate predictors of cognitive abilities.

The remainder of the discrepancy is most likely attributable to specific areas of learning disability as indicated by the subtest scatter. The three areas most impacted are variously cited as reading, spelling, and arithmetic. The impact of these learning disabilities on academic underachievement varies by academic domain and by genetic subgroup. Roof et al. [71] compared the intellectual features and academic achievement of 24 persons with a deletion subtype and 14 persons with UPD. On average, those with UPD had significantly higher verbal IQ scores than those with a deletion. Additionally, verbal IQ scores exceeded performance IQ scores for those with UPD, while those with a deletion evidenced the opposite pattern. When verbal and performance scores are averaged to yield an overall IQ, the IQ scores are not significantly different between the two groups. A study by Milner et al. [73] showed not only some similar but also conflicting data. Average verbal IQ had an 11-point advantage compared to non-verbal IQ in those with UPD; however, those with subtype BP2 deletion had a similar pattern with an averaged 9 point advantage in verbal skills. Like the Roof et al.'s study, full scale IQ was similar for those with the deletion and UPD subtypes; however, those with BP2 deletions outperform those with BP1 deletions by almost 9 points, which suggests that there is variation based on breakpoint type.

Two other studies had similar findings and concluded that, on average, those with a deletion (both deletion types together) do substantially poorer on reading and spelling than do those with UPD, and that there is little difference between the two groups on math skills, which are uniformly depressed [55, 81]. Measures of cognition and academic achievement were also strikingly poorer for those with a type I deletion than for those with a type II [55, 73]. To the extent that these differences exist, they may further reflect differences in brain development due to varying amounts of material on the paternally contributed member of the chromosome 15 pair.

Mathematical abilities in PWS have also been evaluated through standardized arithmetic testing. Testing with the Number Processing and Calculation Battery showed overall impairment in PWS compared to controls; however, the ability was matched in some specific areas, such as dot counting, number comparison, using an analog number scale, and coding written number to words [83]. Remarkably, individuals with PWS outperformed a standard control in using an analog number scale; the significance of this finding is unclear. Differences in genetic subtypes were seen on this study, which is a different conclusion than previously mentioned studies, with individuals with UPD performing comparatively better in many tasks such as number comparison, numerical coding, and mental addition than those with the deletion subtype.

Specific Deficits in Learning, Memory, and Cognitive Processing A number of investigators have examined the relationship between intellectual deficits, academic underachievement, and specific cognitive processing deficits. Findings suggest deficits in sequential processing [84],

visual and auditory attention [75, 84], and short-term memory [11], whereas long-term memory and simultaneous processing appears less impaired [11, 64, 75]. Short-term memory and processing skills may be relatively more preserved in those with maternal disomy [85], though this is preliminary.

There are few studies on learning and memory in PWS. Warren and Hunt [11] found that children with PWS performed less well on a picture recognition task than children with intellectual disability of unknown etiology matched for chronological age and IQ. The two groups of children performed similarly on a task meant to measure access to long-term memory. The authors also compared cognitive capabilities of adults with PWS and controls matched on mental age and IQ. PWS participants with difficulty in short-term memory processing lost more information that was learned over time compared with controls. A study by Stauder et al. [75] extends these earlier findings, documenting that the auditory modality in PWS is even more affected than the visual, and that short-term memory is also impaired. As with other areas of cognitive processing, genetic subtype exerts an influence. The work of Joseph et al. [85] found that visual memory is a specific strength among individuals with maternal disomy. Specifically, they found that the rate of short-term memory decay among individuals with maternal disomy was considerably slower than that of either PWS individuals with deletions or matched controls.

A study by Jauregi et al. [84] replicated similar short-term visual memory differences in PWS; however, it also reported that individuals have more difficulty with sequential visual tasks, and relatively better performance with simultaneous visual tasks, as measured by a battery of neuropsychological tasks. Deficits in memorization were improved with repetition to the point that scores could be improved to those seen in a cognitively matched reference population.

Visual perception, organization, and puzzle-solving skills have been reported as relative strengths in some people with PWS. Taylor and Caldwell [86] reported Wechsler Adult Intelligence Scale (WAIS) subscores for adults with PWS and obese control participants matched for overall IQ. The highest subtest scores for the participants with PWS were on picture completion, object assembly, and block design. Similarly, block design on the Wechsler Intelligence Scale for Children (WISC) emerged as a strength for 9 of 26 children with PWS [82], suggesting that some individuals with PWS have the ability to recognize and evaluate figural relations greater than would be expected based on other aspects of cognitive functioning.

Fundamental visual processing differences between genetic subtypes are suggested by divergent mathematical ability and may be reflected in more basic cognitive-perceptual processes. Fox et al. [87] looked at subtype differences in the discrimination of familiar shapes (square, rectangle) generated through the motion of random elements. While not in normal ranges, the deletion group performed as well as others with non-specific intellectual disability, but the UPD group was significantly worse. However, in a follow-up study using photographs of familiar non-food *and* food-related objects, the UPD group demonstrated better short-term visual memory than the deletion group. Thus the question of subtype differences in basic cognitive processes and intellectual abilities remains open.

Additional cognitive processing differences are suggested in the work by Dykens et al. [64]. Using the Kaufman Assessment Battery for children, the authors report significant sequential processing deficits with relatively stronger simultaneous processing abilities in a group of adults with PWS of mixed genetic origin. This must be considered a tentative finding as the population tested was outside the age ranges for which the test was standardized and normed. Reports of superior puzzle-solving ability in PWS individuals would be consistent with this hypothesis [88, 89].

Looking across the age spectrum, UPD potentially may be associated with a risk of dementia based on the characteristics of individuals seen in a case series study following 8 adults with UPD [78]. A slightly larger cohort study of individuals over 40 showed that 15% (4

of 26) individuals with PWS showed symptoms of dementia, and all were women with UPD and a history of psychosis [90]. Neither studies accounts for any confounders such as medication use or physical health, and more studies are needed before specific conclusions can be drawn; as medical treatment lenghtens the lifespans of adults with PWS, better quantification of the risk of dementia, and the associated risk factors, is important for care for these individuals.

Additional studies of the basic cognitive processes (visual and auditory perception, visual and auditory processing, and memory) and learning styles are critical for designing more effective educational and behavioral programs.

Language Processing Deficits The speech and language characteristics of those with PWS are dealt with at length elsewhere in this volume (see Chap. 9). This section provides a brief summary of these findings as one aspect of the neurodevelopmental and neurocognitive components of PWS. A number of authors document delays in spoken language development [57, 58, 91]. While these delays may, in part, reflect poor muscle tone and reduced breathing capacity leading to reduced oral motor skills, there is a pattern of speech and language deficits that are independent of motor ability. Language development typically follows a progression from hearing and understanding (receptive language) to speaking (expressive language) single words, two-word phrases, two-word sentences, and eventually interactive conversation. A number of speech-related difficulties have been described: (1) delays and deficiencies in receptive language including difficulty with auditory discrimination (later, phonics or sounding out words is usually impaired), (2) vocabulary deficits, (3) suboptimal understanding of sentences [14], (4) limited ability to talk in sentences, and (5) poor understanding and use of language in a communicative context (pragmatic skills). In a study that summarized the language ability of 35 participants with PWS via the Clinical Evaluation of Language Fundamentals-4 (CELF-IV) [92], core language ability was significantly impaired in PWS (mean score 60.4, very low range) with expressive and receptive language significantly lower than verbal intelligence. Those with UPD had discrepant language functioning with higher expressive vs. receptive language ability, which is a pattern seen in autism spectrum disorder. Symptoms of autism spectrum disorder, and patterns seen in genetic subtypes, are further discussed below. Further description of patterns of speech is varied and beyond the scope of this chapter.

As a final note of importance, there is significant overlap in the presentation of language processing and executive function deficits, and teasing these areas apart in PWS is a diagnostic challenge. Authors of a study of 18 adults with PWS concluded that after measurement of executive function tasks and the Digit Span Forwards task, and completion of the Aberrant Behavior Checklist (ABC) and the Dysexecutive Questionnaire (DEX), deficits were consistent with feedback in the phonological loop and phonological memory as opposed to executive function skills [93]. This conclusion is in contrast to what is presented below, but consistent with the variability seen among individuals.

Higher-Order Processing Deficits Higher-order cognitive processing encompasses such abilities as abstract thinking, executive function, and metacognitive abilities. A number of authors describe the concrete thinking style associated with PWS across cognitive capacities. Thus, many affected individuals demonstrate an inability to generalize learning from one situation to another or to see the commonalities across situations, as well as an inability to change perspectives or incorporate new facts even when proven wrong [14, 94]. Simply switching tasks is also a difficulty; this is seen in functional brain imaging studies of task-switching events that demonstrate deactivation in the anterior region of the ventromedial prefrontal cortex in 8 adolescents and adults with PWS [95]. Furthermore, many affected individuals are comorbid for attention-deficit disorder (ADD), demonstrating both attentional deficits and impulsivity in multiple

settings [68, 96]. In a small study on direct measurement of attention, executive function, and visuoperceptual organization, individuals with PWS show consistent impairment compared to a normed population [84]. Sequential processing was noted as a specific difficulty, with improvement with repetition. Differences in these skills were irrespective of intelligence, though this needs further study before definitive conclusion can be made.

Metacognitive abilities are defined as "thinking about thinking" or the use of executive processes in overseeing and regulating cognitive processes. Both the concreteness and rigidity of thinking, combined with attentional deficits and the judgment failures of impulsivity, give evidence to a marked lack of metacognitive processes. As a result, both academic and social functioning in affected individuals are impacted by an inability to mobilize executive functions and use memory, visuomotor skills, language, and judgment in concert to solve multifaceted problems.

Across the Age Spectrum: Adaptive Behavior There has been limited formal assessment of adaptive behavior functioning in persons with PWS. Overall, adaptive impairment is consistently seen across studies, and impairment is often greater than expected based on cognition alone, though further variations in function vary from study to study. This is likely a reflection of the wide variety of cognitive and behavioral challenges that individuals with PWS face, limitations in the number of studies available, and variability in study populations. Taylor [97] reported Adaptive Behavior Scale (ABS) data from an unpublished study conducted by Taylor and Caldwell [86]. ABS scores of adults with PWS were compared with those of a group of intellectually similar, obese individuals without the syndrome; individuals with PWS had scores that were 34% below those of the control group. Next, Dykens et al. [52] evaluated the adaptive behavior profile of adolescents and adults using the Vineland Adaptive Behavior Scales. Daily living skills proved an adaptive strength for the group as a whole, while socialization, particularly coping skills, emerged as a relative weakness. Interestingly, the authors reported that daily living skills become more of a strength with increasing age. Relatively inconsistent data was seen in a study by Milner et al. [73] that demonstrated that individuals with PWS had adaptive function more impaired than predicted solely by cognition, with biggest area of weakness being motor skills; socialization skills via that population sample was actually a relative strength.

As growth hormone treatment has been shown to likely preserve cognition in those with PWS, there is further suggestion that treatment also maintains adaptive function. A 2017 study by Dykens et al. [79], mentioned previously, compared the adaptive function of 43 individuals treated with growth hormone to 130 treatment-naive individuals of ages 4–21. The study demonstrated that participants that received growth hormone had significantly higher communication and daily living skills on the Vineland Adaptive Behavior Scales, 2nd edition. Over a 10-point difference was seen in composite score and all subscales; however, other areas did not show statistical improvement, likely resulting from the wide range of functioning seen across individuals. Adaptive improvement was complicated by a comparable improvement in cognitive testing scores; however, demonstrating causality was beyond the scope of the study.

Impairments in adaptive function are persistent later in life. Results reported by Holland et al. [98] and Thompson and Butler (unpublished data) found that PWS subjects, compared to IQ-matched controls, had substantially decreased competence in their degree of independent community living skills. This may reflect the far more restricted lives led by most individuals with PWS and, therefore, more limited opportunities to develop skills.

Adaptive function, including activities of daily living, physical functioning, and care dependence, may be significantly impaired late in life, i.e., over 50 years old, as seen in a study using the the Observational Questionnaire Elderly Residents with ID (Observatielijst Ouderwordende

Table 8.5 Estimates of adaptive function in Prader-Willi syndrome by genetic subtype

		Composite adaptive behavior score (n)			
Study	Adaptive skill measurement tool	All deletion types	Deletion, BP1	Deletion, BP2	UPD
Milner et al. [73]	Vineland	62.6 (45)	57.6 (14)	64.2 (30)	57.8 (47)
Dykens and Roof54	Vineland		52.9 (26)	60.5 (29)	63.5 (33)

Bewoners, OOB) that compared the functioning of adults over 50 years with PWS to the functioning of younger adult individuals with PWS [78]. Substantial decline in activities of daily living was noted over the age of 50 years. This suggests that premature aging may be an evolving concern, which is especially important to consider as the relative age of individuals with PWS increases.

In addition to evaluating adaptive function by age, there are emerging patterns in adaptive function by genetic subtype, as seen in Table 8.5. Data is again in its infancy and is limited by the above-mentioned factors. Of note, growth hormone treatment status is not described by Milner et al.

Social Interaction, Communication, and Repetitive Behaviors

Etiological Classifications as Obsessive-Compulsive, Developmental Arrest, or Autistic Spectrum Disorder Separate from food-related behaviors and fixations, individuals with PWS exhibit other behaviors that are repetitive, ritualistic, and appear both driven and compulsive. There are separate schools of thought that frame the interpretation of these behaviors, which in turn frames the corresponding clinical response. Given the complexity of the behavioral phenotype, it is of value to those working with individuals with PWS to appreciate all unique frameworks as each provides clinical value. For many people with PWS, repetitive behaviors, obsessions, and social difficulties are sufficiently problematic and disruptive that management and adjustment are negatively impacted throughout the life span. Several authors studying these behaviors assert a genetic tie between PWS and obsessive-compulsive disorder (OCD) [99, 100] and encourage treatment with medications for obsessive-compulsive disorders [101, 102]. Other investigators, however, view these same behaviors quite differently, remaining skeptical of a genetically based PWS-OCD link [98, 103, 104], or attribute symptoms to features consistent with autism spectrum disorder [105–109].

Obsessive-Compulsive Disorder as a Manifestation of PWS Asserting that restricted and repetitive behaviors constituted "full-blown obsessive-compulsive disorder (OCD)," Dykens et al. [99] compared the scores of 91 older children and adults with PWS with an age- and gender-matched (cognitively typical) comparison group who had previously been diagnosed with OCD. The PWS group yielded significantly elevated scores on specific subscales of the Yale-Brown Obsessive Compulsive Scale. These included hoarding, ordering, and arranging objects according to a certain set of rules, and the repetitive "asking or telling" subscales. The scores of the PWS group were comparable both in number and severity to the comparison group. A subsequent study by the same authors found that these characteristics were more severe and problematic in those with a deletion than in those with UPD [110], leading the authors to conclude that the pathogenesis of PWS appears to predispose many individuals to obsessive-compulsive behavior, if not clinically diagnosable OCD [102].

By contrast, Feurer et al. [111] used the Compulsive Behavior Checklist (CBC) to study 53 PWS persons with a deletion and 12 with UPD between the ages of 4 and 41 years. The CBC was designed to gather information about compulsive behaviors specifically in persons with intellectual disability. Their findings indicate that, separate from skin picking, the compulsive-type behaviors observed in those with PWS are a single behavioral dimension

that is quite different in character from classic OCD, and they question the usefulness of applying such diagnostic terms to the PWS population. Common to both sets of studies was the use of volunteer subjects, which likely added a considerable degree of selection bias to both studies.

To avoid the biases associated with a volunteer study population, a recent study attempted to assess *all* persons with PWS residing in a circumscribed geographic region of the United Kingdom [103]. Theoretically, by sampling from the whole population, certain types of bias found in volunteer subject populations are eliminated. Ninety-three persons with PWS ranging in age from 5 to >31 years were compared with 68 intellectually disabled persons of other etiologies on the Developmental Behavior Checklist, the Aberrant Behavior Checklist, and the Vineland Adaptive Behavior Scale. The authors report a specific lack of obsessive symptoms but did observe a high prevalence of ritualistic behaviors in the PWS population. Although ritualistic, these behaviors are quite different in character from those typically described as obsessive-compulsive behaviors or those associated with classic obsessive-compulsive disorder.

Continuing to characterize the behaviors associated with PWS as a variant of obsessive-compulsive disorder is seen by many as counterproductive. Current DSM-V criteria [112, 113] for OCD include the presence of obsessions and compulsions that are time-consuming and/or distressing to the affected individual, based on the recognition that such behaviors are (1) out of the range of normal, (2) negatively impacting the affected person's ability to function, and (3) goal-oriented in reducing or preventing a specific thought or action. While studies clearly document repetitive, ritualistic, and compulsive behaviors as salient characteristics of PWS, *clear evidence of classic compulsions and obsessional thinking is lacking*. This latter argument is frequently countered with an argument that persons with PWS have difficulty assessing and expressing the presence of the internalizing components of obsessions. A more important argument, however, is the clear indication that persons with PWS do not view these behaviors as out of the range of normal, nor do they appear to suffer psychological distress from the presence of these behaviors; indeed it is more often the caregiver who is bothered by these behaviors than it is the affected individual [98]. Recall that these behaviors appear during the same time frame and are similar in character to those found in typically developing children of the same age. Further, children with PWS are distinguished from the typically developing children in that the latter develop these behaviors only transiently, as children with PWS continue to display such behaviors. Thus, Clarke et al. [103] and Holland et al. [98] asserted that the etiology of these behaviors is a "specific pattern of atypical and arrested brain development such that the characteristic rituals and compulsions of early childhood continue and only resolve if development goes beyond that particular developmental phase" [98].

Autism Spectrum Disorder as a Manifestation of PWS A contrasting point of view suggests that the pattern and developmental trajectory of repetitive behaviors are more compatible with autism spectrum disorder. This approach also more broadly incorporates the social communication features that are features of PWS. In 2013, diagnoses that shared features of autism (autism, Asperger syndrome, etc.) were reclassified as autism spectrum disorder under the DSM-V [112]. Diagnostic criteria are persistent deficits that lead to impairment across multiple contexts in (A) each of three areas of social communication and interaction: (1) social-emotional reciprocity, (2) nonverbal communication, and (3) developing, maintaining, and understanding relationships and (B) at least two of four types of restricted, repetitive behaviors: (1) stereotyped or repetitive motor movements, use of objects, or speech, (2) insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior, (3) highly restricted, fixated interests that are abnormal in intensity or focus, and (4) hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment.

Studies before and after the update to the DSM-V directly address the presence of autistic spectrum disorders in PWS. In a controlled study prior to the DSM-V investigating the behavior and personality characteristics in a Swedish population of persons with PWS, Akefeldt and Gillberg [47] administered both verbal and nonverbal IQ tests, problematic behavior questionnaires, and the Asperger Syndrome and High Functioning Autism Screening Questionnaire to 44 persons with PWS ranging in age from 8 months to 36 years. The latter was used as a measure of social skills. Scores ranged from 0 to 54; 19 and above is considered to indicate the presence of autistic spectrum disorders. The group of children aged 8 months to 3 years 8 months had a mean score of 3.4; however, those whose ages were 7 years and up had a mean score of 19.1, indicating the presence of autistic spectrum disorders. Since only mean scores were given, we do not know what percentage of the groups scored in the autistic spectrum range. Both groups scored higher on this measure than a control group.

In a separate study predating the DSM-V and designed to look at autistic spectrum disorders as a unifying behavioral framework, Whitman [104] had parents complete the Autism Behavior Rating Scale, the Gilliam Autism Rating Scale, the Australian Asperger Scale, and the Social Skills Rating Scale, and directly assessed 18 subjects with PWS using age-appropriate IQ tests and a battery of language tests to assess language development, language processing, and pragmatic language. The results indicated that, under the age of 7, all children exhibited a number of autistic features (hand flapping, gaze avoidance, some tactile defensiveness, and abnormal use of language), and 30% qualified for a full diagnosis of autism; by the age of 7, 85% qualified for a comorbid diagnosis of Asperger syndrome or "high functioning autism."

Multiple other studies that have followed have replicated and further demonstrated that standardized clinical tools for autism spectrum disorder are positive in individuals with PWS. This includes behavioral measures such as the Childhood Routines Inventory (CRI) [108] and Affect in Play Scale (APS) [109], and highly utilized diagnostic tools such as the Autism Diagnostic Observation Schedule (ADOS, both the 1st and 2nd eds) [73, 107, 109], the Autism Diagnostic Interview (ADI) [73], Autism Screening Questionnaire (ASQ) [73], and the Social Responsiveness Scale (SRS) [105]. Of particular importance, Dykens et al. [107] looked at a large sample of individuals with PWS (146 individuals) aged 4 to 21 years with the Autism Diagnostic Observation Schedule-2 (ADOS-2) and a clinical diagnostic team and found that roughly 12% met full diagnostic criteria for autism spectrum disorder. At the same time, 76–100% demonstrated repetitive behaviors and/or communication problems that had a demonstrated impaired quality as is seen in autism.

Recent studies that have shown similar diagnostic conclusions have also elucidated differences in genetic mutation subtype. Individuals with UPD have been shown to be more at risk for autism-related features in general [106]. Milner et al. [73] completed a large study looking at 47 individuals with the deletion subtype and 47 with UPD and found that those with UPD had larger deficits in reciprocal social interaction across multiple diagnostic tools for autism spectrum, including the ADOS-2. In the previously mentioned study of 146 individuals with PWS by Dykens et al. [107], 78% of those that met diagnostic criteria for autism spectrum disorder had UPD; however, only 38% of the total study group has UPD; the diagnostic rate in those with UPD was 26% and total study group was 12%.

Genetic association in general also supports a PWS-autism spectrum disorder association. Using ordered-subset analysis, Dementieva et al. [114] identified a homogeneous subgroup of families with autistic spectrum disorders with a primary symptom complex described as "insistence on sameness." DNA studies of the "insistence on sameness" mapped the chromosomal abnormalities to chromosome 15q11–q13. A similar methodology investigated a group of "normal" individuals with diagnosed obsessive-compulsive disorder. These DNA studies mapped OCD to the X chromosome at the FRAXE site, not 15q11-q13. Considering repetitive behaviors

in general, more recent study also suggests that inflexibility is the underlying impairment that leads to repetitive behaviors in some genetic syndromes. Wookcock et al. [66] demonstrated that individuals with the deletion-subtype of PWS (UPD was not included) have difficulty with "task switching" or responding to a specific stimulus under a different set of criteria. The authors also showed that this difficulty with task switching was also associated with parental report of preference for routine. This difficulty is shared with children with fragile X syndrome; however, it is more pronounced in PWS when controlled for intelligence.

Studies evaluating further language ability and autism spectrum features in PWS are sparse. Autism spectrum disorders often present with a unique and developmentally "flipped" language profile, with receptive language being more impaired than expressive language [115]. As mentioned previously, a study looking at language via the Clinical Evaluation of Language Fundamentals-4 (CELF-IV) showed individuals with UPD had discrepant language functioning with higher expressive vs. receptive language ability [92].

Interest in co-diagnosis of PWS and autism-related behaviors is increasing as the practicality of using Applied Behavioral Analysis (ABA) therapy to treat both social deficits and repetitive behaviors is increasingly being considered in multiple neurogenetic disorders, including PWS. It must be stated unequivocally that it is *contraindicated and absolutely inappropriate* to address hyperphagia with ABA, given the altered central mechanisms driving the hyperphagia, rendering ABA principles unsuitable and potentially harmful for addressing this manifestation of PWS. There is emerging evidence that ABA may be helpful for the social deficits that are identified in PWS [105], and as ABA and ABA-based programs improve communication, expressive language, and play skills [116, 117], there are possibly generalizable benefits to those with those deficits and PWS. For further information on specific behavioral strategies and responses in PWS, please see Chap. 12.

Discussing autism-related behaviors in PWS in incomplete without specifically addressing sensory processing differences. Unfortunately, this is an area of significant need for further study, especially as understanding sensory behaviors may help frame appropriate responses to reduce maladaptive behaviors. For example, altered pain perception in PWS is present when compared to typical individuals, and the underlying mechanism is not associated with known physical characteristics or peripheral nerve function based on an evaluation battery composed of electroneurographic examination, sympathetic skin response, serum insulin and glucose levels, and somatosensory evoked potentials [118]. This is important to consider when framing responses to possibly resultant behaviors such as skin-picking or self-injurious behaviors (which are discussed more below).

Social Behavior Across the Lifespan Deficits in social reciprocity are a cardinal feature of autistic spectrum disorder [119]. At the most fundamental level, successfully engaging in reciprocal social interactions depends on two precursor abilities: social perception and social cognition, both of which appear to be impaired in those with PWS. Understanding of emotions and facial expressions has been shown to be a consistent deficit in the communication profile of individuals with PWS. A cohort of 56 individuals with PWS correctly identified only 55% of different facial emotions correctly, with particular difficulty noted in identifying fearful, angry, and disgusted facial expressions [120]. This difficulty is generally out of proportion to what is seen in other syndromes, as children with PWS are in general less able to appropriately identify emotions than children with Williams syndrome and children with cognitive impairments of unknown origin. Similarly, in a study of 94 individuals with PWS, ages 5 to 93, there was consistently noted confusion about interpreting emotions via facial expressions, with noted confusion of "sad" and "angry" expressions [121]. While increased intelligence, increased age, and better attention were associated with better ability to detect social

cues, interpretation was a universal difficulty and judging intention of communication action in context was especially difficult. It is unclear whether there is an effect of genetic subtype on interpretation of facial expression, as those with deletion and UPD have shown to have similar behavioral characteristics, but possible differences in facial orientation and gaze direction on electrophysiological measurement [122]. Higher-level social cognition and interpretation was also identified as an area of weakness in a study of 11 adolescents with PWS, aged 10.1 to 17.1 years. Participants were asked to interpret the intention of characters in stories involving lies, jokes, and broken promises. Few of them were able to identify lies or jokes or to differentiate between a promise broken intentionally or unintentionally, which points to difficulties in interpreting social intentions. Similarly, despite arguing that these behaviors signal a developmental arrest, both Clarke et al. [103] and Holland et al. [98] reported that these behaviors segregate with and correlate most strongly with autistic symptoms.

The appropriate development of play is a core skill for relationship building and is an area of impairment among children with autism spectrum disorder. This is also an area of potential weakness in the development in children with PWS. A cohort of 14 children with PWS and intellectual disability, ages 7–13 years old, shared similar impairments in both individual play and joint-partner play to a matched group of 10 children with diagnoses of autism spectrum disorder and intellectual disability [109]. Measure of play skills in this study was via the Autism Diagnostic Observation Schedule, 2nd Ed (ADOS-2), and a modified Affect in Play Scale (APS). Children with PWS showed lack of play, limited engagement with toys, and limited functional and symbolic play, especially when in self-directed play without a partner.

Overall, generalized social deficits are reported in multiple studies [106]. Specific behaviors reported are varied and include social isolation [123], decreased frequency of reciprocal communication events, limited conversational skills, limited insight of social conventions, and ability to effectively report events [107]. Evidence also suggests that social deficits are more severe in individuals with UPD via measurement with the Social Responsiveness Scale (SRS) and the Social Competence Inventory [105].

Related, sensory processing differences often play a role in social communication. A recent study found that processing of sensory information and the isolation of human voices from background noise are not always accomplished before an adult individual with PWS makes a behavioral response [124]. Consistently altered response time was noted regardless of the stimulus provided, even if it was a picture of food. This phenomenon is especially noted in individuals that have UPD.

Mental Health Symptoms and Diagnoses, and Other Challenging Behaviors

A Bias Toward Measuring Problematic Behaviors From the earliest efforts, behavioral studies have primarily focused on describing and quantifying the development and severity of problematic behaviors and emotional/psychiatric disorders associated with PWS to the exclusion of behavioral strengths. Moreover, many studies include a limited age range measured at a single point in time. Such a methodology makes it difficult to understand age-related behavioral issues and limits the ability to describe behavioral patterns over time. Further, depending on the nature of the investigation, the use of a comparison group may be appropriate, but defining an appropriate comparison group presents additional difficulties [101]. Neurophysiologic and neurogenetic techniques offer an avenue for developing a more complete understanding of the neurobiologic substrate of behavior, but these techniques can be particularly difficult to use with this population. Finally, while differences in neurocognition have been seen in individuals with different genetic subtypes of PWS, studies evaluating behavioral patterns by genetic subtype are limited and have shown significant variability within subtypes without a clear pattern development [110, 125].

Despite these difficulties, studies across time, taken together, provide a broad, general picture of behavior in PWS. Let us look at the various components of this complex behavior as we currently understand them.

Behavioral Patterns and Personality Unlike many other genetic syndromes, the behavior differences among those with PWS appear to be largely independent of gender [126], cognitive level, sleep quality [127–129], or weight, although an occasional study has reported a sex- or weight-specific finding [53, 123, 130]. In a recent study, poor physical health (current or historical) and sensory processing sensitivities also were *not* associated with psychopathology [126]. Low adaptive ability *was* associated with psychiatric illness (via the Anxiety, Depression, and Mood Scale) and specifically was associated with generalized anxiety and manic/hyperactive symptoms, which is inconsistent with prior studies that do not show a relationship between cognition and psychopathology.

As mentioned above, there is limited and conflicting information on the effect of genetic subtype on behavioral traits. Dykens et al. (1999) [110] compared the problematic behavior of 23 genetically confirmed individuals with a deletion and that of 23 age- and gender-matched PWS persons with genetically confirmed UPD. Their findings suggested that, compared with those with UPD, individuals with a deletion had both a greater quantity of and more severe problematic behaviors. Specifically, those with a deletion had more problematic eating behaviors, underactive and withdrawn behaviors, sulking, skin and nail-picking, and hoarding behavior. Those with a deletion also obtained higher severity scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) than did the UPD group. However, when a related research group, Dykens and Roof (2008) [125], studied behavioral patterns of 88 individuals with PWS by genetic subtype (deletion with breakpoint 1, deletion with breakpoint 2, and UPD), there was significant variability within subtypes without a clear pattern development using similar measurement tools. The authors did note that increasing age in those with BP1 deletion was consistently associated with lower problem behaviors within the subgroup, namely attention, aggression, atypical thought, and generalized externalizing behaviors on the CBCL (Child Behavior Checklist), which was not demonstrated with UPD or BP2 deletion. This may suggest that complete deletion of certain genes, namely *CYFIP1*, has a modifying effect on behavior over time. Butler et al. [17] compared 12 individuals with type I deletions to 14 individuals with type II deletions and 21 with UPD. In general, those with type I deletions had poorer behavior and psychological functioning coupled with reduced independent behaviors than those with either type II deletions or UPD. In most, but not all, instances those with a type II deletion scored midway between those with a type I deletion and those with UPD. However, studies by Gross-Tsur et al. [68] and Steinhausen et al. [131] found no behavioral differences between the typical deletion and UPD genetic subtypes. The behavioral impact of genetic subtype appears to be extremely complex, requiring further research to fully understand. Indeed, genetic subtype may have a greater influence on the later development of psychiatric disorders, a subject to which we will later return.

Vogels et al. [76] assessed the *personality* dimensions of extroversion, agreeableness, consciousness, emotional stability, and openness to experience. In general, those with PWS scored more negatively on all dimensions than age-matched controls. This was particularly true for the subdimension of benevolence. A further difference was found between those with the isodisomy form of UPD (two identical maternal chromosome 15) and those with imprinting center defects. The children with isodisomy UPD were significantly more benevolent and conscious (or more empathic and considerate) of others than were children with imprinting center defects. This is one of the few studies to assess personality on standard personality measures.

Not illogically, both early and recent works in this area have been heavily focused on understanding the developmental trajectory, range, and severity of problem behaviors frequently

associated with PWS. There has been relatively less focus on the positive behavior characteristics and personality strengths. In part this seemingly skewed focus reflects a continuing critical need for effective intervention programs. It may also reflect a real characteristic of the behavioral picture associated with PWS, i.e., a tendency toward a "negative" personality profile with a preponderance of difficult behaviors. Multiple studies using multiple behavior measures clearly document that, separate from the food-related behavioral difficulties, affected individuals are more prone to behavioral disturbances including age-inappropriate temper tantrums, stubbornness, skin picking, impulsivity, and ritualistic and repetitive behaviors [4, 52, 99, 103, 130, 132, 133]. Further, the overall rate, severity, and chronicity of these disturbances are frequently more intense than those associated with comparable genetic or cognitive impairments [3, 48, 134] or other obese groups [47]. However, this difficult behavior picture is largely absent for the first few years of life. Indeed, most authors agree that, on the whole, infants and young toddlers with PWS are affectionate, placid, generally cheerful, largely compliant, and usually cooperative. Further, most authors agree that as the hyperphagia emerges, a separate and distinctly negative behavioral shift is also observed [135]. Unfortunately, the historic reliance on hyperphagia for diagnostic confirmation delayed systematic observation of these early behavioral characteristics until genetic technology supported early diagnosis. Thus, until recently, there was little available data regarding the behavioral and emotional characteristics of the first 2 years of life beyond that found in routine medical records. Therefore, the question to be posed is, Is this shift simply a normal developmental process (i.e., the "terrible twos"), or is this an age-related expression of Prader-Willi syndrome, or both?

Behavioral Patterns and Challenges in Early Childhood At least three studies have looked at the nature of behavior changes in toddlers with PWS [47, 136]. Akefeldt and Gillberg [47] examined three groups of affected individuals seeking to determine (1) which behavior and personality characteristics in PWS are primarily linked to the syndrome and not to cognitive levels or weight and (2) whether behavior problems are age-related. The youngest group ranged in age from 8 months to 43 months; a second group ranged from 7 to 36 years of age and had received no medication treatment of any sort (either psychotropics or growth hormone); and a third group ranged in age from 4 years 2 months to 36 years 3 months and had received some kind of medication treatment. An age- and BMI-matched comparison group, approximately half of whom were also intellectually disabled, served as controls. Behavior was measured with (1) the Swedish translation of the Rutter scales, a parent report instrument of behavior problems in the home setting, (2) the Asperger and High Functioning Autism Screening Questionnaire, and (3) the Eating Attitudes Test. All but the youngest group were also administered the Birleson Depression Questionnaire. The youngest group had a mean Rutter score of 2.8 while the two older groups had mean scores of 11.6 and 12.8, respectively. Within the youngest group, parents reported an accelerating interest in food and an increased need for routine beginning around age 2 and a subsequent increased tendency toward stubbornness emerging around age 3. While some of these changes may reflect normal developmental processes (e.g., the "terrible twos"), unlike typically developing youngsters, the data indicate that those with PWS evidence no remission from this stage. Instead the data point to an evolving, increasingly difficult behavioral picture that intensifies with age.

Behavioral Patterns and Challenges in Middle Childhood Individuals with PWS that are of young school age (kindergarten) and older show a specific behavior pattern with characteristic personality traits that are clearly differentiated from controls. This includes skin picking; fussy, overly particular and/or stubborn behavior; insistence on certain routines; aggressive behavior; tantrums; very changeable mood; decreased tolerance of frustration; and preoccupation with food [137]. Many of these behaviors are already present in those younger than age 5; however,

they are more dramatic at this age and more pronounced compared to other genetic syndromes that are often associated with obesity such as Down syndrome [131, 136]. Dimitropoulos et al. [136] further demonstrated that these behaviors are more persistent and permanently increasing by evaluating behaviors in a cross-sectional study of 105 children ranging in age from 2 to 6 years in comparison to age-matched children with Down syndrome and typically developing children via measurement on the Early Child Developmental (age 2) or the Preschool Child Developmental (age 3) Inventories, a tantrum behavior survey, and a Compulsive Behavior Checklist for Clients with Mental Retardation.

Multiple authors have described a second shift of behavior around 7 to 8 years of age. These changes include an escalation of the earlier-described behavioral pattern along with a significantly increased rigidity of behavior [47, 53, 137], including the tendency to "get stuck" on a thought or question; increasing concerns for real and imagined worries; less responsiveness to flexibility, to redirection, or to "calming down until reasonable" alternatives; and a tendency to "fly off the handle." At this age point, both skin-picking and daytime sleepiness stand out as major behaviors that distinguish this group of children with PWS both from younger children with the syndrome and from other age-matched children with mental retardation. At the level of personality traits, parents of children with PWS report their children as less agreeable, having lower emotional stability and openness and showing increased irritability compared with age-matched, typically developing peers [54]. Similarly, "collecting" behaviors and motor stereotyped behaviors noticeably increase in this age group as well [137].

Skin-picking is a behavior of particular importance to note, as it is pervasive in many individuals with PWS and is markedly increased in this age group and subsequently persistent across the lifespan [138]. In a survey by Morgan et al. [139] that included 67 children (aged 5–19 years), greater than 95% of their families reported skin-picking, and approximately 42% of individuals reported at clinically significant levels based on standardized scales. Increased severity of skin-picking had a moderately strong association with increased inattention and impulsivity and decreased quality of life. Some studies ask about a related but more general term "self-injury". When using this term, self injury is reported to be common in PWS at a potentially similar prevalence, with a study by Arron et al. [140] that demonstrated 51.6% of individuals with PWS have self-injury and 43% having physical aggression to others. Behaviors in this study were also associated with impulsivity. Self-aggression behaviors were most commonly described as rubbing or scratching, as opposed to biting or hitting.

Behavior Patterns and Challenges in Adolescence Emotional lability; temper tantrums; skin picking; repetitive, ritualistic, and compulsive-like behaviors; and hoarding become particularly prevalent in adolescents with PWS, distinguishing this age group from both younger children and older individuals with PWS, as well as from typical adolescents [4, 52, 132, 140, 141]. Furthermore, these difficulties persist into early adulthood [3, 5, 77, 130, 142]. Although some behavior modulation is often seen in later ages, problematic behaviors still exceed those seen in other comparison groups, including individuals with comparable intellectual disability [5, 6, 48]. Standardized behavioral tools show clinical concerns for both internalizing and externalizing behaviors in adolescents with PWS, namely anxiety, conduct, and attention problems [6]. Available studies analyzing modifying factors for the development of these disorders in PWS are just emerging and hint at the genetic complexity of the syndrome in the setting of the greater genome. For example, girls and women with PWS with homozygous or heterozygous G703-T polymorphisms in tryptophan hydroxylase 2 (TPH2), the rate-limiting enzyme in the synthesis of serotonin in the brainstem, were shown to have significantly higher internalizing symptoms, namely anxiety and depression, compared to others, in addition to earlier-onset and more severe hyperphagia [143]. While the gene for TPH2 is located remotely from chromosome 15, this suggests that there are many modifying genetic factors to PWS not directly related to the gene mutation.

While prevalent in all age groups, self-injury is noted specifically to peak at this age (defined as 11–20 years old) [140]. Behavior related to inflexibility persists in adulthood to a significant degree. Structured interview of caregivers of both children and adults with PWS reported that the most common antecedent to a tantrum, across the age spectrum, was a change in routine or expectation [96].

Psychotic Symptoms, Psychotic Episodes, and Psychiatric Disorders in Adolescence and Adulthood The presence of psychiatric symptoms and multiple psychiatric disorders has long been associated with PWS [2, 4, 144] with both an incidence rate exceeding that found in a general population of those with intellectual disability and with an excessive predominance of those disorders falling in the psychotic disorder spectrum [7, 145, 146]. And, while research indeed suggests an increased rate of psychotic illness in adults with PWS, the nature of this illness appears to be substantially different in character and duration than that found in a non-PWS affected population [147].

Bartolucci and Younger [148] describe three distinct neuropsychiatric symptom complexes associated with PWS: trait fluctuation, lethargic refusal, and florid psychotic states. The trait fluctuation complex includes exaggerations of behaviors commonly associated with the syndrome, including oppositional tendencies, explosive episodes, and persistent social difficulties. While most individuals with PWS have fluctuations of these traits, for some, this fluctuation has predictable and severe cycles of occurrence, and they may qualify as having a cyclical psychiatric disorder. In a separate cohort study by Descheemaeker et al. [69], a subset of children with PWS who shared this severely fluctuating behavioral pattern were monitored for up to 15 years. Authors noted that these children were often diagnosed with bipolar syndrome during childhood, but after following these children into adolescence and adulthood, many received a diagnosis of psychosis. Subsequently, the conclusion was that "bipolar" diagnosis was more correctly an early manifestation of psychosis.

Bartolucci and Younger's other behavior complexes include lethargic-refusal state, characterized by a sudden onset course of several weeks with withdrawing from usual activities and interactions, a refusal to eat or drink (often with disordered thoughts particularly around the possibility of food being purposely poisoned), a complete inattention to hygiene and self-care often accompanied by a nonorganic incontinence, and remaining totally bedridden, and florid psychotic state consisting of auditory or visual hallucinations, mood disturbances, and delusions accompanied by fear or occasionally abnormal elation. Subsequent investigations of those with symptoms in this latter group have led to the relabeling of this complex as atypical cycloid psychoses [149] and have raised speculation that those with a UPD subtype may be genetically more vulnerable to developing this disorder.

Vogels et al. [76] sampled an older PWS-affected group with known psychiatric problems. The group was divided into those with psychoses and those with mood disorders. The authors then conducted a retrospective review of early childhood behavior patterns and found that those with psychoses and either UPD or an imprinting center defect had an early childhood behavior pattern that was "active and extroverted." Those with mood disorders, all of whom had the deletion form of PWS, had a childhood behavior pattern of "passive and introverted." The authors note that these two behavior patterns are the extremes of a continuum. Many with PWS fall somewhere on a line between these two extremes. A subsequent population-based study in the UK found five young adults with PWS and psychoses. Since these young adults all were of the UPD genetic subtype, the assertion that UPD inevitably leads to psychoses has emerged [150]. Along the same lines, a recent report examining the mental health trajectories of individuals with PWS over the age of 50 showed that all (8 of 8) individuals with UPD had a psychiatric diagnosis and psychotropic medication use, with all but one have a diagnosis with psychosis or psychotic features [78]. All (4

of 4) individuals with deletion were without a history of a psychiatric illness. Underlying structural differences may be related to differences in phenotypic presentation based on subtype. A recent study showed that the white matter microstructure in children and adolescents with UPD was reduced in most major white matter tracts, which is a shared finding with individuals with schizophrenia and/or significant psychosis [151]. White matter tract changes were more subtle in those with the deletion subtype.

Those with a deletion subtype may also be at risk for significant mental health illness. Verhoeven et al. [149] indicated that a subset of affected individuals with the deletion subtype appeared to be more vulnerable to serious mood disorders, among them bipolar disorder. While psychotic disorders are dramatic in presentation and call for immediate intervention, acute and recurring mood disorders are far more prevalent in this population [69, 152] and may account for the majority of those described as the TF subgroup by Bartolucci and Younger. Clinical observations suggest that independent of a genetic vulnerability, the previously described cognitive rigidity, combined with difficulty labeling and expressing feelings and poor coping skills, may predispose those with PWS to an increased incidence of mood disorders, particularly when a major loss is involved. While genetic subtype may be associated with specific expressions of psychiatric difficulty, it seems much more fruitful to understand the nature of environmental stressors that catapult a small subset of individuals with PWS into these more serious psychiatric disturbances. Research regarding this association is ongoing.

Summary and a Challenge for Improvement

In this chapter, we have attempted to summarize the current understandings and empirical underpinnings of the neurodevelopmental and neuropsychological aspects of PWS as they present clinically and functionally across the lifespan of individuals with PWS. Further understanding of risk factors, prognostic signs, and patterns of medication responses is imperative in order to provide appropriate therapeutic and medication supports and to minimize mismanagement. Prioritizing behavioral research and improving understanding are necessary for optimizing outcomes for individuals with PWS across the lifespan.

It has been a decade since a previous version of this chapter was written. In that decade, extensive research has contributed to a broader and more in-depth description of these aspects of PWS; at the same time not only has this increased knowledge failed to answer basic questions, but it has also increased our understanding of the extreme complexity of this disorder and raised more questions than answered. It is the authors' hope that when this chapter is rewritten a decade from now, a much more definitive understanding of this complexity will be forthcoming.

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9 Speech and Language Disorders Associated with Prader-Willi Syndrome

Roxann Diez Gross

Introduction

The speech and language skills of individuals with Prader-Willi syndrome (PWS) differ greatly in the severity and type of deficits that they present, ranging from individuals who are nonverbal to those who acquire normal speech and language skills by adulthood. Swallowing dysfunction (dysphagia) has also been identified as an important comorbidity in PWS, and it is associated with increased risk of premature death from choking and pulmonary infection. Due to the low incidence of the disorder—1 in 10,000 to 15,000 individuals [5, 7]—professionals such as speech-language pathologists, physical therapists, and occupational therapists may encounter only a few individuals with Prader-Willi syndrome in their practice. An understanding of the characteristics of Prader-Willi syndrome that may impact speech, language, and swallowing abilities will allow the professional to evaluate each individual for potential contributing factors to communication deficits and to plan appropriate intervention strategies. Recognition of the likelihood of subclinical (without symptoms) dysphagia will reduce the risk of pulmonary infection and choking incidents related to deglutition (eating food and drinking liquids).

We turn first to the issues surrounding swallowing followed by those surrounding speech and language concerns for those with Prader-Willi syndrome.

Swallowing

National and international surveys that have sought to identify causes of premature death in PWS have reported that obesity-related health problems may not be the most common cause of premature deaths [2]. In a review of 486 deaths in the United States, Butler and colleagues determined that respiratory failure and respiratory infection, aspiration, and choking were the most common causes of death [6]. One of the most likely explanations for respiratory-related mortality is linked to swallowing dysfunction, and

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the shared anatomy between breathing and swallowing.

The ability to swallow safely is often misunderstood and, generally, taken for granted. Some reasons for this disregard are because swallows are so rapid and require little awareness. In fact, early anatomic animal studies inaccurately concluded that swallowing was a basic reflex that required no sensory information. Conversely, research efforts over the past 30 years have determined that, in humans, swallows are not simple reflexes like knee jerks or gags. Indeed, each swallow is a highly complex act requiring a multitude of muscles and nerves to rapidly and exquisitely time interactions between the sensory and the motor systems of the upper airway. When an impairment is present in the sensory and/or motor system related to swallowing, safe and efficient transport of food and drink from the mouth to the stomach is jeopardized, and a medical condition called "dysphagia" occurs. Persons with dysphagia are at increased risk to suffer from life-threatening pulmonary infections and choking death. For those with PWS, sensory impairment, hypotonia, muscle weakness, and respiratory insufficiency place them at high risk for dysphagia.

Hypotonia in infants with PWS results in obvious feeding disturbances; however, the symptom of silent aspiration, or liquid entering the trachea and lungs without the appearance of a cough, had only been postulated. It was not until 2017 that direct observation of aspiration in infants with PWS was reported. In a retrospective review of videofluoroscopic (X-ray movie) swallowing studies performed on infants ranging from 3 weeks to 29 months, Salehi and colleagues identified silent aspiration in 87% of the swallows that were recorded [26]. They also observed that liquids remained in the pharynx (throat) after swallowing, which is an important risk factor for aspiration. Based upon their findings, the authors recommended that all infants with PWS receive a comprehensive feeding and swallowing evaluation. The dysphagia of infancy was thought to resolve once hyperphagia begins; however, additional research has revealed that subclinical (without symptoms) dysphagia can persist into adulthood.

Concerned that the high rate of aspiration and choking-rated deaths in PWS could signal underlying swallowing problems, Gross' research team prospectively studied swallowing function in a group of 30 volunteers who ranged in age from 5 to 35 years [16]. Participants randomly swallowed measured and spontaneous amounts of thin liquid (water with barium powder) and a soft solid (cookie with barium baked in) while swallowing was recorded using videofluoroscopy. The data revealed that, despite the lack of overt symptoms or complaints, dysphagia was present in all participants.

The results of the research study identified several risk factors for aspiration and choking. One important finding was the failure of the cookie to be transported through the throat and into the esophagus. In some cases, the amount of residue that remained in the pharynx was severe; yet, when questioned, subjects had no awareness or sensation that the food had not "gone down." Pharyngeal residue is particularly risky for choking and aspiration because the airway closes for the swallow, but then quickly reopens so that breathing can resume. The open airway is vulnerable for invasion if the liquid or food do not enter the esophagus. In addition, the frequency that participants inhaled rather than exhaled after each swallow was much higher than the frequency that has been measured in typical subjects of all ages.

Exhalation after the swallow is important because it has the potential to clear any material that may have entered the larynx (voice box). Post-swallow exhalation is also an indication that there was a sufficient amount of air in the lungs during the swallow. Should a large amount aspiration occur, adequate lung volumes are needed to clear the airway via the expiratory or "aspiration reflex" which results in an immediate and forceful exhalation. On the other hand, post-swallow inhalation can draw residue into the airway, and insufficient air in the lungs will trigger

the cough reflex which begins with deep inhalation causing aspirated material to go deeper into the lungs.

The timeliness of swallow onset is also important, particularly with liquids. Liquids are typically held within the mouth and transported into the throat simultaneously with the onset of the swallow. In the PWS participants, a delay between the oral and pharyngeal swallowing phases was observed where the material rested in the throat before the swallow occurred rather than the typical overlap. Silent aspiration was observed to occur during the delay because the airway is only closed during the swallow.

The most striking study finding was the presence of cookie stasis in the esophagus of all 30 participants. Furthermore, none of the participants had any awareness or sensation that the esophagus remained distended with the swallowed cookie, and none made any attempt to clear the material. Figure 9.1 shows an example of esophageal stasis. The combination of undetected esophageal stasis, combined with hyperphagia and rapid intake (gorging), greatly increases the risk of prandial aspiration and asphyxiation. Entry of solid food into the lungs can occur if the esophagus contracts to expel stasis upward, and as previously stated, the airway is open while breathing. In addition, because the trachea (windpipe) and the esophagus are in close proximity to one another, airway blockage can occur if the esophagus is so full that it extends into the trachea and occludes the airway. In this instance, the Heimlich maneuver will not help because the food is in the esophagus, and the maneuver relies upon using air pressure in the lungs to blow out a blockage in the larynx. Fortunately, compensatory strategies for incomplete bolus clearance are available.

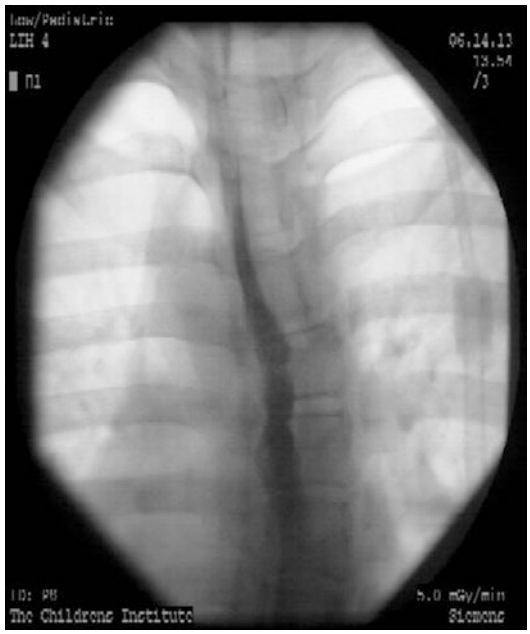

Fig. 9.1 Chest X-ray of a 13-year-old person with PWS showing that a barium cookie that was swallowed did not enter the stomach (esophageal stasis)

As previously noted, solids and liquids were given randomly during the study; consequently, it was observed that when a 10 cc or larger liquid bolus followed a solid, the pharyngeal residue and esophageal stasis cleared. This observation led to the development of a therapy called "Pace and Chase" where persons with PWS were taught to take a drink of a liquid after swallowing one or two bites of solid food. Clinically, this technique was used during modified barium swallowing studies of patients with PWS and found to be effective for both pharyngeal and esophageal food clearance. Figure 9.2 is an example of the instructions that can be used to teach the Pace and Chase compensatory strategy.

In summary, persons of all ages with PWS are very likely to have significant subclinical dysphagia and silent aspiration. Swallowing impairments, including esophageal clearance, can only be detected using visualization techniques such as videofluoroscopy. It is recommended that all persons with PWS receive a modified barium swallowing evaluation, especially anyone who has a history of choking and/or pulmonary infection. Furthermore, because esophageal stasis can result in the misdiagnosis of rumination or regurgitation, careful attention to esophageal clearance of solids during the swallowing study is required. We turn now to the parallel concerns of speech and language development.

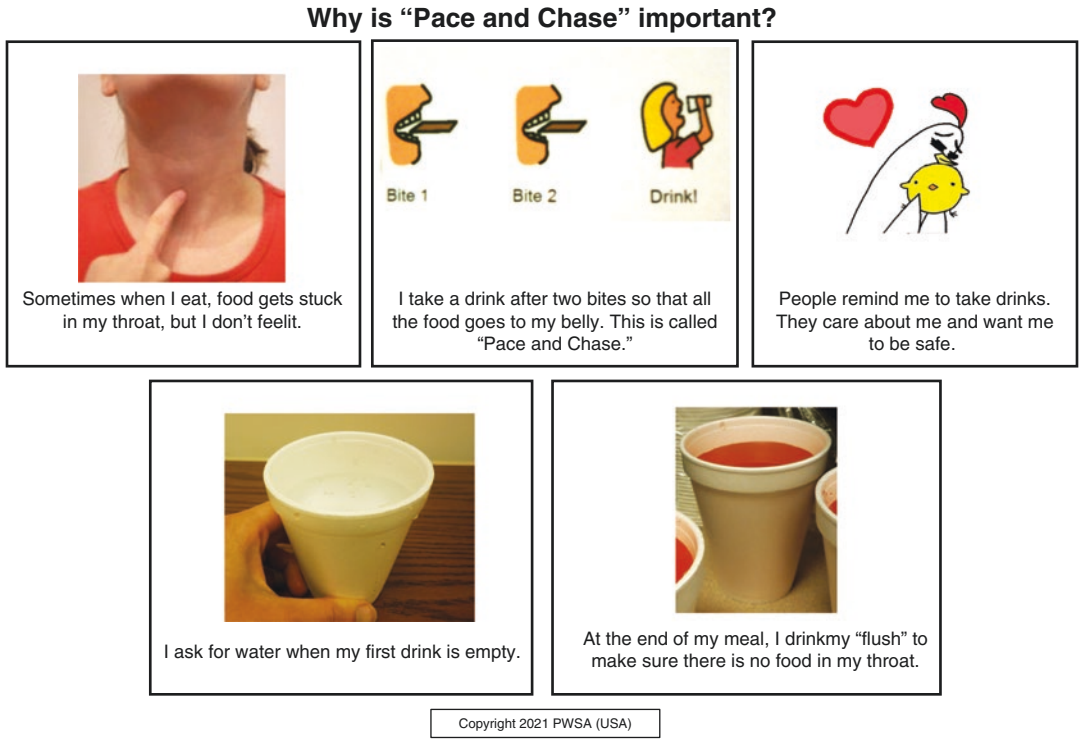

Fig. 9.2 Teaching the pace and chase technique

Speech and Language Characteristics

The speech and language skills of individuals with Prader-Willi syndrome are reported to be below expectations based on intellectual levels [4, 15, 20, 24]. Although great variability exists in the speech and language skills of individuals with Prader-Willi syndrome, several common features have been noted. These include poor speech-sound development, reduced oral motor skills, and language deficits. Speech is often characterized by imprecise articulation, hypernasality, flat intonation patterns, an abnormal pitch, and a harsh voice quality: most of which are typical of flaccid dysarthria. Prosody, or the melody of speech, may also be disrupted. In addition to these speech difficulties, the individual with Prader-Willi syndrome may have language problems. Language problems include deficits in vocabulary, grammar, morphology, narrative abilities, and pragmatics (Table 9.1).

Speech-Sound Development A distinguishing feature of PWS is poor speech-sound development. Speech-sound disorders likely have a genetic basis and in PWS may be linked to chromosome 15q14, (which has also been connected to autism and Angelman syndrome) [14, 28]. Speech-sound disorders include both errors of articulation or phonetic structure (errors due to poor motor abilities associated with the production of speech-sounds) and phonological errors (errors in applying linguistic rules to combine sounds to form words). Individuals with PWS may exhibit deficits in either articulation, or phonology, or both. Several factors may account for the poor speech-sound development of individuals with PWS, including oral structure abnormalities, abnormal saliva [17, 31], hypotonia, poor phonological skills, and cognitive deficits. Reduced breath support for speech may also be noted. Oral structures of the mouth and jaw that may impact articulation skills include a narrow overjet, a narrow palatal

Table 9.1 Clinical features of PWS and their potential impact on speech, language and swallowing abilities

Clinical feature	Impact on speech/language	Impact on feeding/swallowing
Oral cavity		
High palatal arch	Difficulty to accurately produce certain phonemes	Impaired bolus preparation, palatal residue
Micrognathia	Difficulty to accurately produce certain phonemes	Impaired mastication
Salivary abnormalities with reduced flow rate and thick, sticky saliva	Reduced speech rate, shortened phrasing	Impaired bolus preparation; oral, pharyngeal, and esophageal stasis Tooth decay
Larynx		
Altered growth	Pitch variations	
Reduced or weak true vocal fold approximation/closure	Breathiness, hoarseness	Aspiration during the swallow
Reduced sensation		Silent aspiration, lack of awareness of food remaining throat and esophagus
Hypotonia/weakness		
Impaired velar motion	Hypernasality, hyponasality	Nasal reflux of liquids Pharyngeal residue and increased risk for aspiration
Tongue weakness	Imprecise articulation	Weak suck, reduced oral bolus control
Pharyngeal (throat) muscle weakness	Vowel distortions	Pharyngeal residue and increased risk of aspiration
Esophagus		Poor bolus transport and clearance
Respiratory system	Short phrasing, low volume	Impaired breathing-swallowing coordination
Sensory system impairments		Dysphagia, absent gag reflex
Cognitive		
Intellectual impairment	Delayed receptive/expressive language skills	Increased risk for more severe dysphagia, difficulty acquiring and maintaining skills to compensate for dysphagia
Sequencing problems	Poor narrative skills	Difficulty acquiring skills to compensate for dysphagia
Behavior disturbances		
Excessive interest in food, hyperphagia		Rapid eating rate with increased risk for severe dysphagia and choking death
Stubbornness, manipulativeness, argumentativeness	Poor pragmatic skills	Difficulty complying with treatment strategies

arch, and micrognathia. However, it is more likely that poor oral motor skills, especially reduced tongue elevation for speech and slower alternating movements of the articulators, account for poor speech-sound skills in PWS [1, 4, 20]. Speech characteristics are often similar to those reported for flaccid dysarthria [20]. Speech-sound errors that have been noted in individuals with PWS include sound distortions and omissions, vowel errors, simplification of consonant blends, and difficulty sequencing syllables. Phonemes that are motorically complex, such as /s/, /r/, /sh/, and blends are usually the most difficult [20]. As with most speech-sound disorders, single word utterances are often more intelligible than conversational speech, and the phonetic environment of the target sound can greatly influence speech intelligibility. For example, an individual might have difficulty producing the "r" sound in the word *crab* when it is preceded by the "qu" sound in the phrase "quiet crab's claws."

Other authors [14] have postulated that poor speech-sound development is the result of poor phonology skills, a component of a more general language deficit in PWS. Downey and Knutson [12] report that most individuals with PWS present with delayed speech-sound development

characterized by phonological patterns typical of younger, normally developing children. However, some individuals demonstrate atypical patterns such as a phonological disorder or an apraxia of speech [24].

Apraxia of speech is a severe speech-sound disorder that includes impairments in syllable sequencing, prosody, and speech-sound characteristics. Although the etiology of apraxia of speech is not well understood, it is presumed to result from impairment in the motor programming aspects of speech-sound production [27]. Rare cases of apraxia of speech have been reported in individuals with PWS. Children with apraxia of speech often do not develop intelligible speech until well into school age. Augmentative/alternative communication intervention (AAC—e.g., sign language and communication boards) may be employed to eliminate some of the frustration that the individual experiences in communication. AAC systems allow the individual to build vocabulary and pragmatic language skills while oral speech skills are developing.

Voice Characteristics The voice of the individual with PWS may differ in pitch, quality, intensity, and resonance from that expected for his/her age and gender. Voice characteristics reported for individuals with PWS include a high-pitched voice, harsh/hoarse voice quality, inadequate vocal intensity, and hypernasality [1, 12]. Hypotonia and altered growth of the larynx may result in a pitch that is too high or low. Nasal resonance may be disrupted by sluggish velopharyngeal movement and/or inadequate velopharyngeal closure potentially due to hypotonia and muscle weakness. Poor velopharyngeal functioning may result in hypernasality, nasal emission, nasal snorting, weak plosive consonant sounds, and unusual manner of sound productions. Although hypernasality is most frequently reported in individuals with PWS, hyponasality has also been noted [23]. Growth hormone therapy, often utilized with PWS individuals, may also affect voice characteristics [21]. Surgical procedures such as those employed for children with cleft palates (e.g., a pharyngeal flap) may reduce hypernasality and improve speech intelligibility. It should be noted, however, that often speech-sound errors persist even though hypernasality has been reduced.

Fluency Dysfluent speech is commonly observed in persons with PWS, but without the secondary characteristics that occur with true fluency disorders (stuttering and cluttering) [10, 12]. Clinical observations of conversational speech suggest that interjections, revisions, and word repetitions may be related to cognitive and language deficits [20]. A slow rate due to poor oral motor skills and a monotone may disrupt the flow and melody of speech.

Language Skills Individuals with PWS frequently demonstrate poor receptive and expressive language skills, with expressive language often more impaired than receptive skills [4, 20, 24]. Analysis of conversational speech samples indicates that individuals with PWS employ a shorter mean length of utterance (MLU) than their peers. Several authors have described patterns of cognitive strengths and weaknesses frequently observed in PWS that might impact language abilities [13]. Specific deficits have been reported in auditory short-term memory [13], linear or temporal order processing, and auditory verbal processing skills [9]. Poor speech-sound development may also affect language skills. For example, the acquisition of grammatical markers (morphology) may be delayed both because the child cannot produce the /s/ phoneme to form the plural and because the child does not understand the concept of plurals [12].

Few studies have examined narrative skills of individuals with PWS. Narratives are accounts of events either real or imaginary. Narratives include storytelling, scripts, schema, and episodic memory. Narratives contain a chronological sequence of events and causal relationships. For an individual to use narratives successfully, he/she must form a topic-centered story, use specific vocabulary, sequence events within the story, describe relationships between people and events, and use correct story grammar. Story grammar includes a

setting, a beginning, reaction, goal, attempt, outcome, and ending. Narrative skills are essential to social development as they promote conversational skills. In addition, good narrative skills are necessary for academic success as they promote reading and writing, develop organizational skills, and build linguistic abilities.

Clinical observation suggests that both children and adults with PWS have great difficulty with story retelling tasks. One study [22] examined the narrative abilities of 19 individuals with PWS, ages 3–30 years. A simple story entitled "The Fox and Bear" was read, and the individual was asked to retell the story. Participants showed deficits in recalling grammar elements and content items and had difficulty answering both factual and inferential questions about the story. While poor language skills may account for some difficulty with narratives, deficits in other cognitive skills such as temporal sequencing abilities, auditory short-term memory, and poor auditory processing skills may also contribute [9, 13]. While narrative skills appear to develop into adulthood, the narrative abilities of the individual with PWS lag behind other language skills. Poor narrative skills may contribute to deficient conversational skills in adolescents and adults with PWS and thus impact social and job-related communication skills.

Pragmatic deficits, including problems with maintaining a topic, judging appropriate proximity to the conversational partner, and turn taking, have also been observed [12]. Pragmatic skills may be influenced by a number of behavioral disturbances frequently noted in individuals with PWS [30]. For example, temper tantrums, compulsive behavior, and skin picking may interfere with peer relationships. Children with PWS have difficulty with social relationships. Sullivan and Tager-Flusberg [29] demonstrated that children with PWS were less likely than IQ-matched children with Williams syndrome to show appropriate empathetic responses. A study of 30 adults with PWS reported perseverative speech, and the findings were replicated in a larger study of 100 persons with PWS [8, 19]. Such pragmatic deficits may impede progress in therapy. Pragmatic language skills may vary by activity, routine, and environment. In adulthood, poor pragmatic language skills may create difficulties in the workplace and with interpersonal relationships.

Written Language Skills Surprisingly, despite oral language deficits, individuals with PWS show relative strengths in written language skills. Strengths associated with PWS include vocabulary knowledge and reading decoding (i.e., sounding out words) [13]. However, some individuals may present with poor reading comprehension skills possibly due to language deficits as described above. Visual spatial skills that have been reported as a relative strength [13] may also contribute to good reading decoding ability. However, variability has been noted in these patterns of strengths and weaknesses. Curfs, Wiegers, Sommers, Borghgraef, and Fryns [9] reported that 10 of 26 subjects with PWS had performance IQs at least 15 points higher than their verbal IQs, 3 had verbal IQs at least 15 points higher than their performance IQs, and 13 subjects did not show any discrepancy. In summary, individuals with PWS present with speech, language, and cognitive deficits that impede their communication skills.

Developmental Course of Speech and Language Skills in PWS

The speech-language pathologist may become involved with the child with PWS soon after birth. In infancy, children with PWS present with a weak cry and early feeding difficulties most likely due to hypotonia. Reduced babbling and signs of early language delay are often observed. All children begin acquiring word understanding essentially from birth (receptive language). Among typically developing children, expressive language follows soon after with cooing at 3 months, babbling at 6 months, and consonants in the form of "dada" and "mama" at around 8 months. For most, by 10 months of age, "dada" and "mama" are used discriminately, and there is evidence that the child understands the meaning of the word "no"; by 12 months of age, most children have acquired at least two words in addition

to "dada" and "mama." By contrast, children with PWS are 18 months of age before they begin to verbally evidence a vocabulary, combine words, and develop early syntax. A substantial number of affected children are much later in acquiring speech; some may be as late as 6 years of age. Oral motor skills remain poor and children exhibit many speech-sound errors that result in unintelligible speech. Pragmatic difficulties may be noted due to poor social skills and the emergence of behavioral disturbances. If the child's speech is highly unintelligible, AAC may be considered, including sign language or communication boards. AAC is usually transitional until oral speech abilities improve, and it alleviates some of the frustration that the child and caretaker may experience.

At school age (6–12 years), children with PWS are usually enrolled in speech and language therapy through the school. Articulation errors remain, with children less intelligible in connected speech than in single words. Receptive and expressive language skills lag behind those of their peers. Voice problems, as described above, may be observed as the child produces longer utterances. As noted previously, reading decoding emerges as a relative strength and children often become fluent readers. However, language difficulties may result in poor reading comprehension.

In adolescence and adulthood, the individual with PWS may continue to demonstrate communication difficulties including residual articulation errors, vocabulary deficits, poor conversational and pragmatic skills, and inappropriate pitch. Some individuals with PWS do achieve normal articulation skills. The individual with PWS may exhibit behavioral traits that are disruptive to good communication skills such as inappropriate laughter. Continued work on conversational speech is essential to adjustment and success in the workplace. Emphasis should be placed on functional language skills and life-skills training.

Previous research on the speech and language skills of individuals with PWS has been based on a small number of individuals and has not examined the developmental course of the speech and language disorder. Many studies have not distinguished between speech-sound errors due to poor oral motor skills and structural deviations and errors due to phonological deficits. One study that attempted to associate speech and language characteristics to a particular chromosome 15 abnormality (i.e., paternal deletion, uniparental disomy, or a translocation) was completed by Dimitropoulos and colleagues [11]. In their study of 35 persons with PWS, formal testing of language ability was performed using the Clinical Evaluation of Language Fundaments-4 (CELF-IV). Expressive and receptive language scores were not significantly different between the genetic subtypes; however, they found that within their uniparental disomy group of 14 participants, expressive language scores were better than receptive.

Summary of a Clinical Research Study A study of the speech and language abilities of a relatively large cohort of individuals with PWS representing three age groups (infant/preschool, school-age, and adolescent/adult) was undertaken. The details of this study are reported elsewhere (see Lewis, Freebairn, Heeger, and Cassidy [23]). The findings of this study are summarized below to illustrate the variability and range of speech and language skills found in individuals with PWS.

Participants The participants were 32 individuals (16 males and 16 females), ages 6 months to 42 years. All met the diagnostic criteria for PWS [18], and diagnoses were confirmed by chromosomal analysis.

Measures Measures were selected to assess oral motor skills, articulation and phonology, receptive and expressive language skills, prosody/voice characteristics, reading, and narrative abilities. Assessments included standardized tests as well as a spontaneous speech sample analysis. Standardized tests varied according to the age and intellectual abilities of the individual.

A rating scale was adopted to summarize data across various age and skill levels. The speech and language skills of each subject were rated

independently by two licensed and certified speech-language pathologists. Receptive and expressive language, articulation, oral motor skills, fluency, narrative ability, and reading skills were scored as normal, mildly impaired, moderately impaired, or severely impaired. Pitch was rated as normal, high, or low for a participant's age and gender, based on criteria proposed by Boone and McFarlane [3]. Voice quality was rated as normal, soft, harsh, hoarse, or strained. Resonance characteristics of speech were rated as normal, hypernasal, or hyponasal. The rate of speech was classified as slow, normal, or fast. A monotone quality to the spontaneous speech sample was also noted.

Results and Conclusion All participants reported a history of communication difficulties and/or were enrolled in speech and language therapy. A majority of the children (83%) received speech therapy prior to the age of 3 years, all had received therapy during the school-age years, and two (20%) continued to receive speech therapy into adolescence and adulthood. This suggests that therapy needs for the individual with PWS are identified early and required for most individuals across the life span.

Oral motor deficits and associated speech-sound disorders are prevalent in the PWS population, with 90.6% demonstrating mild to severe oral motor deficits including poor tongue mobility, shortness of palate, and incoordination of the articulators (see Table 9.2). Mild to severe articulation impairment was observed in 92% of the participants, with younger subjects more severely impaired. A variety of sound substitutions and distortions as well as phonological processing errors were noted. This supports previous suggestions that the speech-sound errors observed in PWS are the result of both poor oral motor skills and concomitant language deficits.

As predicted, receptive and expressive language deficits based on age normative data were observed in the majority of individuals, with 90.5% presenting with receptive language delays and 91.7% presenting with expressive language delays. In addition, vocabulary, pragmatic, and narrative deficits were observed. However, most of the participants who were school-age or older were able to read fluently (83.3%). Reading comprehension was not assessed. Future studies should examine reading comprehension abilities relative to reading decoding skills.

Ratings of pitch and nasality revealed great variability. Thirty-five percent of the participants presented with a high pitch, 30% with a low pitch, and 35% with a pitch appropriate for their age and gender (see Table 9.3). While hypernasality was frequently observed (70.6%), hyponasality was also noted (17.6%). It is not known whether the same factors that contributed to the hypernasality (hypotonia and oral structure) also contributed to the hyponasality that was observed. Further research is needed in this area.

Comparisons between age-matched individuals with uniparental disomy (UPD) and individuals with chromosome 15q deletions were inconclusive. On two of the speech-language measures, UPD subjects received better ratings than did the deletion subjects; on two other measures, the deletion subjects received better ratings than did the UPD subjects; and in one

Table 9.2 Speech characteristics and deficits in individuals with Prader-Willi syndrome

Speech characteristic	Ratings of speech characteristics percentage of subjects (*N*)			
	Normal	Mild	Moderate	Severe
Oral motor skills[a] *N* = 29	9.4%	31.3%	31.3%	18.8%
Articulation skills *N* = 25	8%	12%	36%	44%

[a] 9.2% of participants could not be tested but did have oral motor difficulties

Table 9.3 Voice characteristics in individuals with Prader-Willi syndrome

Voice characteristic	Ratings of voice characteristics percentage of subjects (*N*)		
Pitch *N* = 20	Normal 35%	Low 30%	High 35%
Resonance *N* = 17	Normal 11.8%	Hyponasal 17.6%	Hypernasal 70.6%

case, the ratings for the UPD subjects were comparable. Further research is needed to draw associations between the type of chromosome abnormality and the clinical presentation.

Therapeutic Implications

The individual with PWS will require the services of a speech-language pathologist from infancy through adulthood. A team approach that includes an occupational therapist, physical therapist, dietitian, psychologist, physician, speech-language pathologist, genetic counselor, social worker, and educational specialist provides the optimal management strategy for the child or adult with PWS. Early intervention begins in infancy with a focus on improving oral motor skills for feeding. Continued monitoring of speech and language skills is important as the degree of hypotonia changes over time [24]. Assessment includes standardized and nonstandardized measures to assess oral structures and functions, speech-sounds, and receptive/expressive language skills. Later, with the development of conversational speech, voice, fluency, and resonance characteristics may be assessed.

It is essential that the speech-language pathologist be aware of the unique characteristics of the syndrome that may impact on speech-language development. For example, in some children, drooling is a sign of poor oral motor control. However, children with PWS seldom drool due to reduced saliva output. The speech-language pathologist may incorrectly assume that oral motor skills are intact since drooling is not observed. Further, reduced saliva output may cause dental decay. Table 9.1 summarizes some of the characteristics of PWS that may contribute to speech and language impairment along with potential impact on swallowing function.

In addition to articulation and language therapy, intervention should emphasize social skills and the pragmatic use of language [12]. As shown in Table 9.1, many of the behavioral characteristics associated with PWS impede good pragmatic language ability. Early and ongoing training of social skills will assist the individual with PWS in maintaining appropriate social and interpersonal interactions.

Caretakers and professionals should also be aware of the wide range of communication deficits that are associated with PWS. Therapy should be tailored to address the specific speech and language deficits observed, rather than employing a cookbook approach. Therapy should include an emphasis on the development of oral motor skills. Imitation of movements of the tongue, lips, jaws, and palate may be incorporated into games (see Orr [25] for oral motor games for children). Oral motor skills may be trained in both speech-sound and nonspeech activities. Isolated movements may be mastered first, followed by sequential and motorically complex movements of the articulators.

Future Directions

The speech and language skills of individuals with PWS have not been as well described as those of syndromes with a higher prevalence, such as Down syndrome. While individual case studies have been useful in outlining some of the characteristics of the speech and language disorders associated with PWS, such case studies have failed to describe the great variability of these skills found in PWS. Larger cohort studies are needed to understand the range of speech and language skills that individuals with PWS present. Specific cognitive strengths and weaknesses associated with PWS may impact the speech and language skills of an individual with PWS in a unique way. Comparison groups of children with similar IQ ranges may be employed to highlight the distinctive aspects of PWS. Therapists and other professionals should be acquainted with the features of PWS that may potentially influence communication development. Therapy programs designed for children without PWS may not be appropriate for the child with PWS. As new medical treatments are employed with the PWS population, such as growth hormone treatment, continued research is needed to determine its impact on speech and language. Therapy strategies may be modified to augment these medical interventions.

Glossary

Apraxia (of speech) Nonlinguistic sensorimotor disorder of articulation, characterized by impaired capacity to program position of speech musculature and sequence of muscle movements for the volitional production of phonemes.

Articulators The teeth, lips, and tongue, as they are involved in the production of meaningful sounds.

Aspiration When nongaseous material enters the airway and reaches below the true vocal folds.

Bolus Food to be or being swallowed.

Cluttering Speech characterized by overuse of fillers, rapid rate, and word and phrase repetitions. Unlike stuttering, the individual is usually unaware of the difficulty.

Deglutition The act of swallowing food.

Dysphagia Difficulty or discomfort when swallowing.

Flaccid dysarthria Faulty speech production due to motor difficulties resulting from muscle weakness, characterized by imprecise articulation, hypernasality, breathiness, hoarseness, and short phrases. Rate of speech is usually within normal limits.

Interjections The insertion of extra sounds or words that do not add to or modify the meaning of the sentence, such as "you know" or "like."

Larynx The upper part of the trachea (windpipe); contains the vocal cords.

Micrognathia A small jaw.

Morphology The form and internal structure of words; the transformation of words in such ways as tense and number.

Nasal emissions Airflow directed via the nasal cavity that passes out the nose rather than the more normal route, through the oral cavity.

Nasal snorting Airflow directed into the nasal cavity producing a snorting sound.

Perseveration Automatic and involuntary repetition of a behavior and/or prolonging behaviors that are associated with younger stages of life into adulthood.

Pharyngeal flap A surgical procedure designed to correct velopharyngeal insufficiency.

Phoneme The smallest unit of sound in any particular language; the English language designates approximately 44 different phonemes.

Plosive consonants p, b, t, d, k, and g.

Prandial Relating to a meal.

Velopharyngeal Of or relating to the structures of the soft palate and the pharynx.

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10 Motor and Developmental Interventions for Prader-Willi Syndrome

Toni Goelz

Introduction

From the neonatal period into adulthood, physical therapy is an important component of the multidisciplinary approach to managing the care of the individual with Prader-Willi syndrome (PWS). Physical therapy, as a profession, assumes a role in the "diagnosis and treatment of movement dysfunctions and the enhancement of physical health and functional abilities" [1]. From birth through adulthood, persons affected with Prader-Willi syndrome (PWS) are subject to postural, movement, and developmental dysfunctions. The low muscle tone and absence of normal primitive reflexes in the neonate (newborn) with Prader-Willi syndrome prevent typical movement and postures. Thus, during the child's early development, even the most fundamental milestones are delayed (Table 10.1). The preschool years herald the onset of obesity at about 3 years of age [2]. The early onset of obesity, particularly if unchecked, impacts movement and activity, and it is largely credited with delayed neuromotor developmental milestones and gait abnormalities [3]. The school years often add challenges from learning and behavioral deficits that can be further complicated by motor deficits. By adolescence, the cumulative impact of gravity and poor motor, postural, and muscular development significantly challenge both the spine and most joints. If not previously encountered, in adulthood, sleep is frequently disrupted by respiratory problems and decreased oxygen saturation. Further, osteoporosis substantially raises the risk for fractures in adults with PWS. Since physical therapy intervention at each of these life stages can prevent and remediate obstacles to function and independence, optimal and comprehensive care of infants, children, and adults with Prader-Willi syndrome dictates physical therapy as one of the disciplines providing care. Of equal or even greater importance, the physical therapist is another team member who can support and educate parents and caregivers navigating the challenges and joys of the child with Prader-Willi syndrome from infancy through adulthood.

All infants with Prader-Willi syndrome should be evaluated and followed for intervention by physical, occupational, and speech therapists. The diagnosis of Prader-Willi syndrome is a de facto identification of the risk for delay and with that identification, intervention can begin. Currently, all states in the United States have early childhood developmental intervention programs that serve children from birth to the age of 3. During the birth to 3-year-old period, there can be much overlap between the motor interventions

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Table 10.1 Developmental milestones [10]

		Typically developing child	Child with Prader-Willi syndrome	Child with Prader-Willi syndrome treated with GH prior to 15 months of age
Motor	Independent sitting	6–8 months	11–12 months	Insufficient data
	Crawling	8–12 months	15–18 months	Insufficient data
	Walking	9–18 months	24–27 months	18–24 months [6, 7]
Language	First words	10–12 months	18–72 mos. [5]	14–17 months [6, 7]

provided by a physical therapist and those provided by an occupational therapist. The speech therapist, who may also be enlisted to work on feeding with the neonate, may stay involved to assist with speech and language skills at the 12-to-24-month level. At the age of 3, children are transitioned to early childhood programs in their local school district to continue the goals of developmental intervention for those children still in need.

This chapter provides an in-depth examination of the neuromuscular and concomitant developmental concerns resulting from PWS across the life span and highlights the role of physical therapy interventions for these concerns. It should be noted that over the past two decades, growth hormone (GH) treatment has become standard of care for persons with PWS. Growth hormone treatment of infants and children with PWS has three demonstrated effects that impact physical function: (1) increases in linear growth velocity (skeletal growth); (2) normalizes the size of the hands and feet; and (3) improves muscle mass and tone. These effects are more pronounced when GH treatment is started before 2 years of age as compared to later childhood. However, the age at which GH treatment is initiated varies considerably, with some practitioners choosing to delay treatment until later childhood [4–7].

When GH treatment is started in infancy, while there *may* be rapid improvement in the rate of neuromotor milestone achievement (e.g., sucking, swallowing, head control, sitting, ambulation) attributable to improved functional muscle mass, this is not uniformly observed [8, 9]. If GH is started later in childhood, the consequences of improved functional muscle mass may be less dramatic but still significant. However, regardless of the age at which it is started, GH treatment will not normalize muscle function nor eliminate the need for physical therapy intervention.

Birth to 3 Months As with many congenital disorders, evidence of Prader-Willi syndrome typically presents in utero. Fetal movement that is both limited and of low velocity frequently is reported by the second trimester. "Newborns with PWS showed a lower mean birth weight by one-half kilogram, and a shorter mean birth length by 1 cm, than healthy neonates" [11]. Both decreased fetal movements during pregnancy and depressed Apgar scores at birth result from the low muscle tone, or hypotonia, which is the most classic presenting characteristic of the neonate with Prader-Willi syndrome. The hypotonia may also account for a decreased state of arousal and poor respiratory responses in the neonatal period. Further, the newborn with PWS may be remarkably inactive, with none of the unorganized responses to auditory and visual stimuli or the expected reflexive, random movements. Primitive reflexes—including the sucking reflex—may be decreased or absent. Newborns with PWS usually cry weakly or not at all, reflecting weak respiratory and oral motor musculature, as well as energy conservation.

Inadequate oral motor control results from low tone through the face and mouth, combined with a poor sucking reflex and easy fatigability. It is this inadequate oral motor control that is the etiology (cause) of the early feeding difficulties prevalent in newborns with PWS. Perhaps no frustration is as profound as the inability of the infant to receive, or the parent to provide nourishment to their child during this time when brain growth and development demand adequate nutrition. No caretaker should have to struggle with

this dilemma without the support and assistance of professionals skilled in techniques for remediating feeding difficulties. In addition to physical therapists, occupational therapists and speech therapists can provide assistance in special handling and feeding techniques and have access to an arsenal of feeders, nipples, and other gadgets to facilitate oral motor skills and success with nourishing. Early use of GH may also help improve feeding difficulties.

For an infant with normal muscle tone, the first 3 months of life are characterized by early acquisition of control over reflexive movements and strengthening in gravity-eliminated postures—those postures in which the body does not encounter the full force of gravity, such as side-lying. By contrast, for the child with PWS, marked delays in achieving the midline control and early antigravity positioning normally expected by 3 months of age result from the hypotonia. Neuromotor intervention during these first 3 months focuses on achieving midline awareness (e.g., hand to mouth), midline posture and skills (holding head in the middle of the body), and on teaching stabilization techniques by way of weight bearing through the upper extremities and trunk.

Cognitive and perceptual growth depend on an infant's ability to attend to stimuli by body orientation—typically orientation to the midline—and on an infant's ability to be successful with early motor feedback by batting at toys, by shifting eyes and head position, and by smiling and babbling. By 3 months of age, the typically developing infant begins to recognize the potential for interaction between his body and what he sees, hears, and feels. Hand-eye awareness becomes evident as a baby brings arms toward the midline to bat at objects he sees (see Fig. 10.1). Activation of arms and legs in response to auditory stimuli signals cognizance of voices and noisy toys. A baby's early babbling and oral motor responses to a cooing admirer represent first successes in the area of speech and language. For the 3-month-old with PWS, low tone, an inability to orient to the midline, and an inability to stabilize posture—even with gravity eliminated—alters or even prevents those vital early perceptual and interactive experiences. Therefore, effective motor interventions also must incorporate the needs of the perceptual modalities: vision, hearing, touch, and taste.

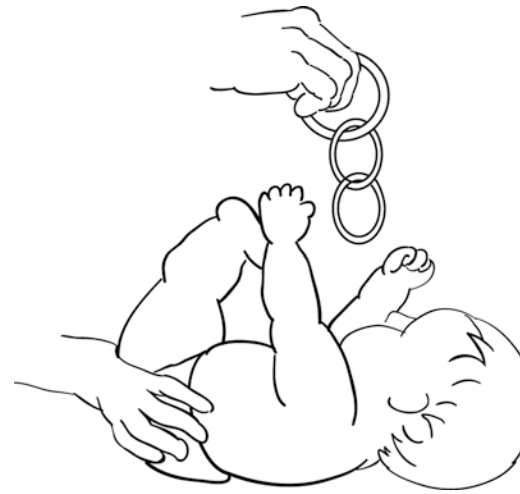


Fig. 10.1 Midline skills

Since early motor interventions that may be critical to long-term outcomes depend on appropriate recognition of need, it follows that the most important variable for a child at risk for developmental delay—regardless of the etiology of the delay—is the early identification of the potential for delay and the immediate onset of intervention. Standardized testing of baseline skills provides the basis for objective measurement of progress. The Prechtl [12], Gesell [13], and Peabody Developmental Motor Scales II [14] are three tools that can be used to assess babies as young as the neonatal period.

3–6 Months For infants benefiting from normal muscle tone, the third through sixth months of development herald the first motor successes against gravity and the first experiences with mobility. Typically developing children learn stability through the shoulder and pelvic girdles by the third month, providing a foundation for building the strength that will control the body that has to compete with gravity. During the second 3-month period, most babies learn to roll from back to tummy, to sit with as little as just guarding assistance, to push up from lying on the

tummy to peer over the top of the crib's bumper pads, and to marine crawl. Gross motor accomplishments are accompanied by rapidly emerging fine motor skills. By 6 months of normal development, most babies successfully extend their reach into all planes, grasp toys with the thumb side of the hands, and orally explore all items grasped.

Most 3-month-old infants with Prader-Willi syndrome have not yet developed stabilization techniques; therefore, they should not be expected to have either the head and neck control (Fig. 10.2) or the shoulder and abdominal strength to roll, nor will they be able to assist with supported sitting. Most will remain very dependent from the tummy position and may not attempt raising the head and neck against gravity. Weakness and instability at the shoulder girdles interfere with midline play. Expect a 3-to-6-month-old baby with Prader-Willi syndrome to grasp a toy directly placed in hand but not consistently to bring the toy to the midline for simultaneous visual, oral, and tactile explorations.

Positioning devices at this age can benefit both babies and caregivers. Molded seats and side-lying devices (Fig. 10.3) can be very valuable for positioning the infant to midline and to begin upright positioning against gravity.

Every opportunity to handle a low-tone baby during this crucial period of development is a positive chance to improve postural stability throughout the child's life. Involvement of physical and/or occupational therapists should continue and may even need to intensify during the third through sixth months. If scarcity of therapists prevents direct delivery of regular services, the therapy staff can be relied upon to educate caregivers on handling and techniques to facilitate achieving developmental milestones. Parents should be able to rely on the therapy staff for guidance and information as they navigate the challenges of nurturing a special needs child.

6–9 Months From 6 to 9 months, a typically developing baby continuously strengthens the abdominal, shoulder, and hip musculature. Rolling matures into a controlled and segmented

Fig. 10.2 Head lag

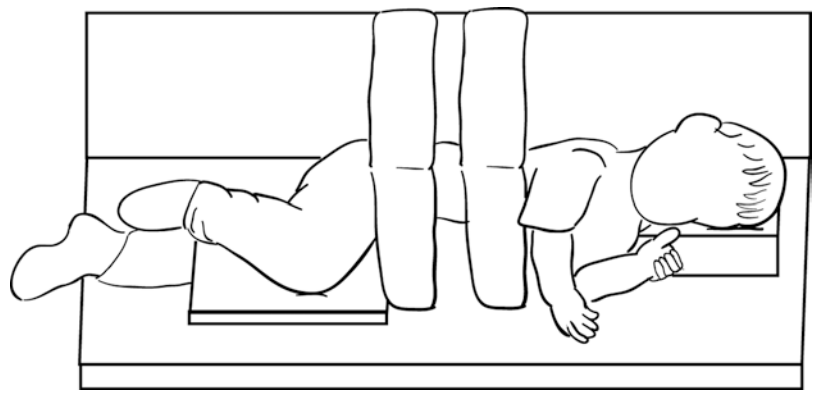


Fig. 10.3 Side lyer

Fig. 10.4 Segmented rolling

process (Fig. 10.4). Sitting is now independent and confident. Mobility is accomplished by efficient marine crawling and by scooting and pivoting in sitting. All-fours rocking lays the groundwork for mobility from all-fours. Maturation to the thumb side of the hand and forearm enables a grasp involving the thumb and index finger. Rotation of the forearm provides a mature communication between the right and left upper extremities. Normal strength and tone through the oral motor structures enable proficiency with spoon-feeding and nutrition through finger-feeding. Babbling and imitation of intonations and sounds are normal expectations and important precursors to spoken words.

The 6-to-9-month-old baby with PWS has probably developed supine to side-lying rolling skills. Rolling is likely to be initiated with a hyperextension of the head and neck and executed without segmentation. While the pattern of movement for rolling may not be optimum, this accomplishment is major and is often reflected in the child's obvious joy at this very early mobility.

Early success in the prone position often follows success with rolling. However, because of the hypotonia, the subsequent difficulty stabilizing the shoulder girdle for weight bearing, and the inherent weakness of the trunk and shoulder musculature, the baby with PWS struggles in the tummy position. Expect the baby to be intolerant when positioned prone. Expect the child to require assistance supporting weight on the forearms and lifting the head to and beyond horizontal. Positioning a baby in prone with a small roll at the chest assists with prone extension and makes the prone-on-elbows position a less daunting task for a child who might otherwise feel defeated in the tummy position. Though lacking the confident elongation and stabilization of normal development, the baby will eventually learn to position against gravity by stacking the head on the shoulders and weight bearing on elbows held close to the chest.

In the absence of optimum strength through the antigravity muscles, the child with Prader-Willi syndrome is unlikely to sit independently before 12 months of age. Positioning the 6-to-9-month child with PWS in supported sitting facilitates the development of a sitting posture and early balance awareness. The caretaker's positioning hands should be held proximally (high on the body) as needed—even to the shoulders and neck (Fig. 10.5). As the baby gives feedback that he can manage the postural challenges, the hands-on support should be moved distally (to a point lower on the body) to appropriately challenge postural skills.

Weakness against gravity is also reflected in a lack of progression through fine motor skills. Even at 9 months of age, most children with

Fig. 10.5 Head holding

PWS, even some who are treated with GH, have insufficiently developed shoulder and upper body strength to support arms against gravity and are unlikely to have the strength to extend the wrists against gravity. Without antigravity wrist extension, reach and prehension patterns are unable to progress.

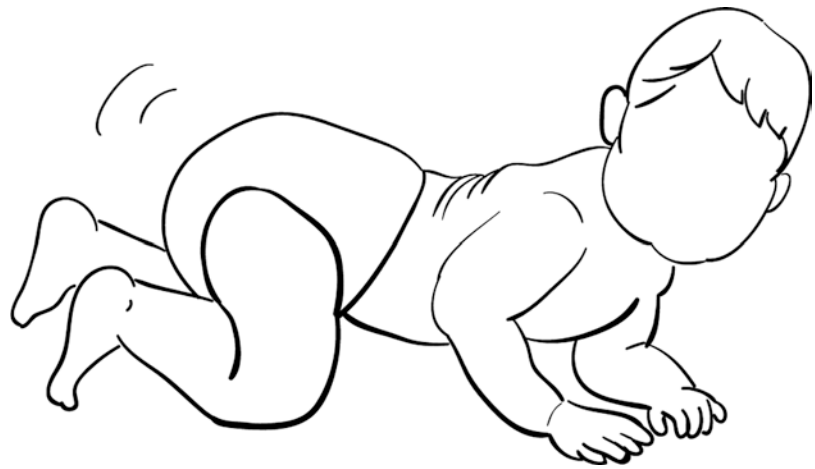
Many parents of 6-to-9-month-old babies with PWS may be unaware that feeding problems still exist. Nonetheless, in all likelihood, the problematic mechanics of feeding persist. The parents and the baby have simply learned to compensate and to work with the challenges. Feeding skills may be reevaluated at this juncture to ensure that nutritional needs are still being adequately met. Because of continuing oral motor issues, the 9-month-old child with PWS may remain remarkably quiet uttering immature verbalizations only infrequently.

9–12 Months When antigravity strength has evolved, and a normally developing child has laid the groundwork for normal movement patterns and postures, the 9th through 12th months signal boundless opportunities to get up and go. By 10 months of age, the child is transitioning into and out of sitting, scooting and pivoting in sitting, and accomplishing mobility in the all-fours position (Fig. 10.6). At 11–12 months, the child begins pulling to standing, cruising along furniture, practicing independent standing balance, and preparing the foundation for independent ambulation. In the fine motor realm, a neat superior pincer (thumb and index finger grasp) and a controlled voluntary release enable play with blocks, puzzles, books, and crayons. These fine motor skills facilitate higher learning and manipulation of environment. Oral motor maturation at this time is signaled by independence with finger-feeding and drinking from a cup, accepting spoon-fed table foods, and independent attempts to spoon-feed. Single words said spontaneously and with meaning emerge at 12 months.

On average, the baby with PWS will, if placed, sit independently by 12 months of age. Because of strength and balance deficits, the child's early sitting is likely to be accomplished with supplemental gross stabilization techniques. Further, instead of an upright posture with elongation through the neck and trunk, the child with PWS is likely to persist with a forward flexed (slumped) trunk posture, a posteriorly tilted pelvis, and shortened neck with head-stacked posture (Fig. 10.7). This child will require the stabilization of arm propping much longer than a normotonic child will.

By 12 months of age, the child with PWS is typically independent with rolling. Expect that, even at 12 months, the rolling skills of a child with PWS will still be accomplished with neck and upper-trunk hyperextension and with little or no segmentation.

Fig. 10.6 Crawling



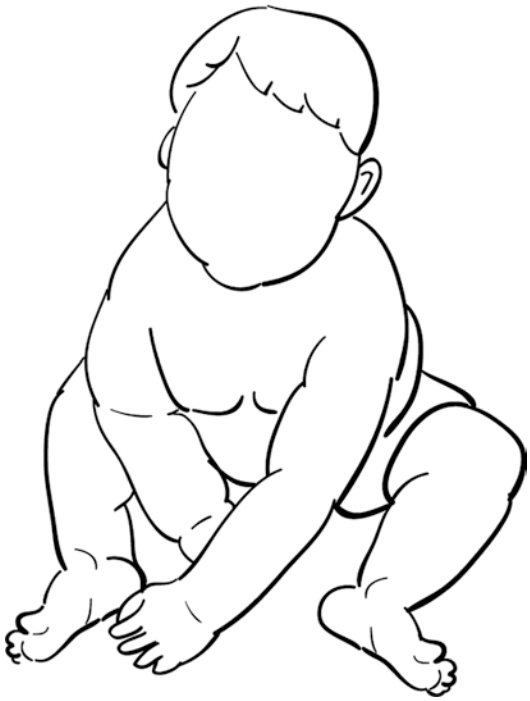


Fig. 10.7 Forward flexed sitting

During age 9–12 months, the child with PWS may have early success on all-fours, and even commence a form of all-fours mobility. Because of the low tone and accompanying postural weaknesses, the child will struggle to accomplish simultaneous weight bearing on hands and knees. Some stabilize themselves by using their head to help support the weight. Hips are likely held in a widely abducted—almost frog leg—posture. If a child with PWS is accomplishing mobility from the prone or all-fours position by 9–12 months, mobility is not likely to feature the segmentation and reciprocating quality of normal development. A bunny-hopping or inch-worming quality is the more likely expectation.

By 12 months of age, if the child with PWS is placed in a standing position, the standing will likely be accomplished with the lower extremities stabilized by locked knees (Fig. 10.8), with a wide base of support, and with heavy reliance on the upper body leaning on a stationary support. The ability to independently pull to standing is often delayed well beyond the time that the child has gained confidence with supported standing.

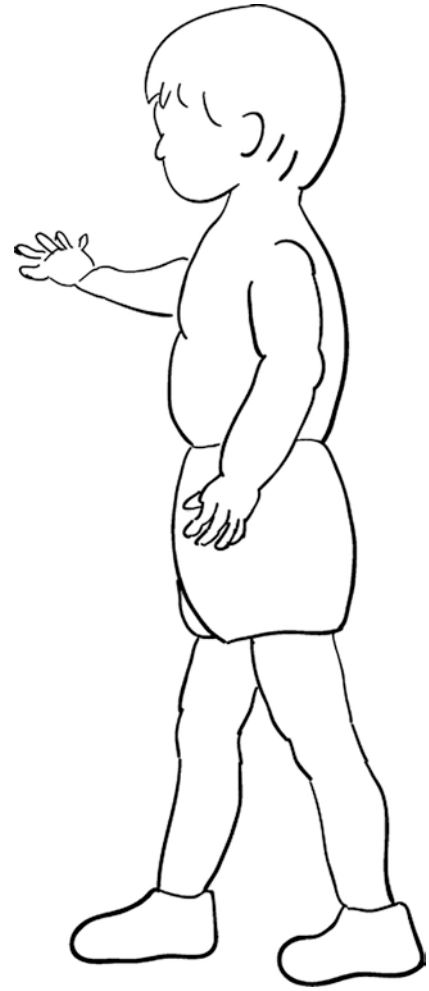


Fig. 10.8 Locked knees

The progression of fine motor skills for this child is very contingent upon mastery of balance and on strengthening the shoulders and upper body. The propping required in early sitting precedes the wrist extension required for fine motor maturation. However, as long as the child relies on his arms for propping, his opportunities to use his arms and hands to reach, to grasp, and to manipulate the environment remain limited.

At 12 months of age, most babies with PWS remain very quiet, with limited babbling and without the single-word utterances of a normal 1-year-old, although with early growth hormone treatment wide variability in early speech development has been observed.

Frequent weight checks to ensure that the 1-year-old with PWS is still gaining weight and maintaining his or her growth curve remain imperative.

Twelve months is an appropriate age to initiate standardized testing if testing has not already begun. Most standardized testing—such as the Peabody Developmental Motor Scales II—can be repeated at 6-month intervals.

12–18 Months Twelve to 18 months is the time in normal development when toddlers align their upright posture and refine their gait. Two to 3 months after a child begins ambulating without assistance, he will begin to demonstrate a heel strike at initial contact and an arm swing. Expect the normally developing toddler to stand with much anterior pelvic tilt of pelvis—giving the child the typical exaggeration of the curve of the low back. When the toddler begins climbing over obstacles on the floor and climbing up stairs or onto furniture, he begins strengthening the muscles of the pelvic girdle, which will ultimately tilt the pelvis posteriorly and lead to the posture associated with appropriate spinal curves.

At 12–18 months of age, the child with PWS who has not yet begun treatment with growth hormone will likely continue demonstrating gross and fine motor delays of 50% or more. In all likelihood, the child will sit independently. However, regardless of GH treatment, the level of independence and the quality of sitting will vary greatly. Some children may be independent by propping if placed in sitting. Other affected children may be transitioning to sitting, maintaining sitting without upper extremity support, and demonstrating an ability to pivot and scoot for sitting mobility.

When the child with PWS begins transitioning to sitting, it will likely be by transitioning without segmentation and by pushing back through the hips, often into a reverse tailor, or W-sitting position (Fig. 10.9). It is best to avoid the reverse tailor sitting position. Reverse tailor sitting position enables sitting without abdominal stabilization and interferes with the development of gluteal strength and the normal pelvic position. Decreased or absence of normal hip external rotation range, postural deficits, and delays in maturation of gait patterns are often attributed to reliance on reverse tailor sitting—even in the normal population.

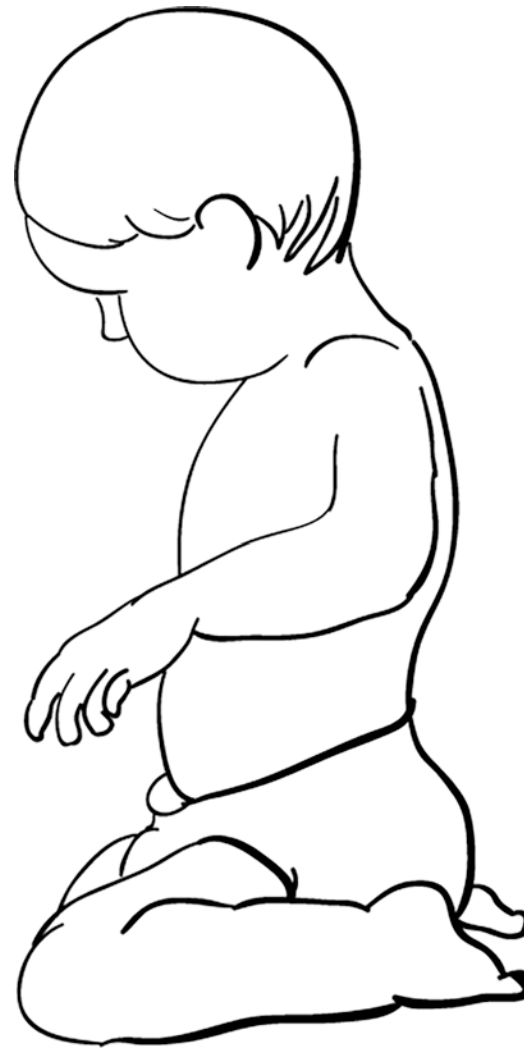


Fig. 10.9 W sitting

Mobility in the prone or all-fours position is a realistic expectation for most children with Prader-Willi by 18 months of age. The quality of prone mobility may vary from marine or tummy crawling accomplished with forearms and inner thighs to all-fours creeping. The influences of hypotonia and the associated weakness will

likely remain evident in the upper extremities, which may still be locked at elbows and elevated at the shoulders. Hypotonia will be evident in the lower extremities by a broadened base of support and by lack of reciprocated movement.

With increasing independence against gravity, balance awareness evolves. With improved balance, the child is able to release upper extremities from their need to prop the torso. With the upper extremities freed of propping responsibilities, the child with PWS has increased opportunities to practice fine motor manipulations. Fine motor progression at this point in maturation is most profoundly challenged by the low muscle tone of the forearms, wrists, and digits.

During the child's second year, the feeding difficulties subside and weight gain stabilizes. Continued monitoring of the child's growth to ensure that the growth curve is maintained remains essential.

Therapy goals for a 12-to-18-month-old child with PWS emphasize balance and strengthening of the shoulder and pelvic girdles. Sit skis can be used to discourage reverse tailor sitting and to facilitate abdominal function. Slanted stools, gym balls, and simple benches can be used to challenge sitting balance against gravity. Opportunities to short sit on benches and small chairs offer alternatives when reverse tailor sitting is difficult to discourage. The prone position also offers important options for strengthening shoulder and pelvic musculature. Whether used to give the child a ride, or propelled by the child's own power, scooter boards are important tools to encourage effort and enjoyment from the prone position.

Speech and occupational therapists should continue monitoring and strengthening oral motor musculature and skills to promote achievement of feeding and speech goals.

18–24 Months By 2 years of age, a child with normal motor development can skillfully jump up and down and forward. Most will ascend and descend stairs from standing—usually by placing both feet on each step. A previously wide-based gait now features a narrow base of support, and heel strike at initial contact is reliable at 2 years.

A child with Prader-Willi syndrome will likely begin to ambulate independently at about 24 months of age; some children receiving GHRT may begin to ambulate as early as 18 months. However, 24 months remains the predominate reported age of walking across most studies of early GH treatment. Gait patterns are immature and typical of an early toddler gait—characterized by a wide base of support, small steps, and anteriorly tilted pelvic posture (Fig. 10.10). In those with normal motor development, body structure and movement patterns change as strength increases and as the child experiences gait and movement through space. By contrast, continued low muscle tone and subsequent insufficient extensor muscle strength may continue preventing the child with PWS from achieving normal maturational progression of posture and gait. In addition, because many children with PWS experience slow growth in utero, during

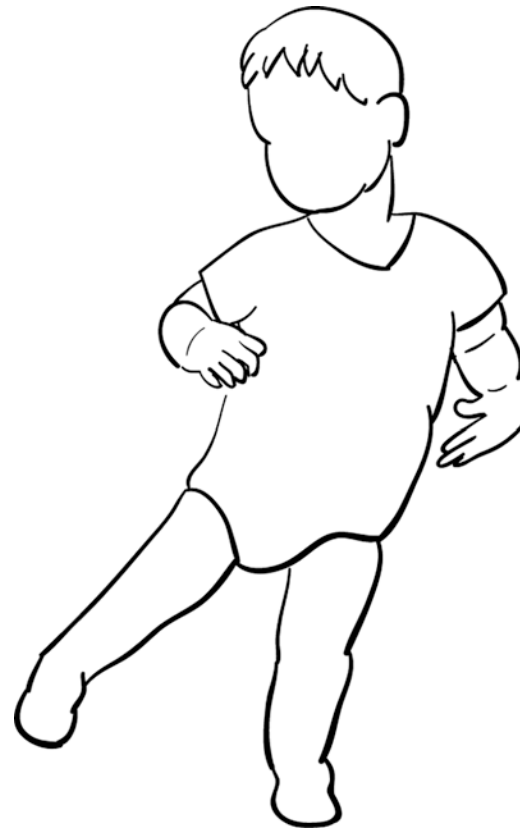


Fig. 10.10 Wide-based gait

infancy and through early childhood, without GH treatment, linear growth deficits may be another factor limiting skeletal development. Efficiency of locomotion is contingent upon normal linear growth of the skeleton.

The physical therapist working with affected toddlers is likely working on goals to facilitate postural stability and independence with standing and gait. Interventions may include adjunctive orthotics for feet and ankles. The orthotics may be as simple as UCBLs (University of California Berkeley Laboratory shoe inserts), which address pronation by stabilizing the heel. The orthotic of choice might be an SMO (supramalleolar orthotic), which offers a greater degree of frontal plane support. For children whose hypotonic lower leg muscles require ankle support in the sagittal plane, an ankle foot orthosis (AFO) can prevent excessive ankle extension.

24–60 Months The typically developing child's rapid rate of growth between the ages of 2 and 5 years moves the child's center of gravity closer to the lower extremities [15]. This child demonstrates locomotion skills reflecting muscle tone, strength, and length that ensures balance and equilibrium. Thus, by age 3, the normally developing child can ascend and descend stairs with alternating feet and without need for handrail assistance. By age 4, most can hop on one foot and can tandem walk on a line on the floor. By age 5, most can skip, can balance on one foot for 10 s, and can perform sit-ups. During this same early childhood period, the gross and fine motor delays of the child with PWS become less glaring. By age 2, some children with PWS have enough muscle strength and control to achieve ambulation and mobility milestones. However, though the child may be walking, climbing, and transitioning, these skills lack quality, maturity, and refinement. This is especially impacted by age at which GH treatment is initiated. Assessment on a standardized test, such as the Peabody Developmental Motor Scales II, will define the delays more specifically.

Problems compound for the child with PWS during the early childhood period, as this is the time associated with rapid weight gain [16]. Particularly at this age, rapid weight gain for a child with PWS typically does not represent muscle growth and length or height. Even with the support of GH treatment, for the child with PWS, at this age the growth of body fat often exceeds the growth rate of bone and muscle leading to the need for a specialized diet that balances growth needs with caloric restrictions. The challenges of managing posture, equilibrium, and mobility increase when weight gain further compromises limited strength, muscle tone, and short stature.

The physical therapist working with the preschool child with Prader-Willi syndrome should define goals to strengthen the proximal and core musculature and to challenge endurance. During this period of rapid weight gain, aerobic activities not only address muscle tone but also boost metabolic rate and increase energy expenditure. Scooter-board play, games of wheelbarrow, crab walking, climbing skills (on simple playground equipment or on more sophisticated rock walls), riding toys, swimming, and water play are all gross motor activities that strengthen muscles and challenge aerobic capacity. Horseback riding, or hippotherapy, can be a very beneficial activity for children as young as preschool age. Therapists use horses as therapeutic aids to address muscle strengthening, balance and equilibrium, sensorimotor, conditioning, postural, and even speech goals [17].

The occupational therapist should be evaluating and remediating deficiencies in activities ranging from grapho-motor skills, to perceptual skills, to dressing and activities of daily living. Similarly, at this point, speech therapists should be assisting the child with PWS with articulation deficits as well as with language content.

From Preschool Through Adolescence In those developing typically, the center of gravity continues to lower as body length progresses to adult height. Muscle bulk and strength guide the body's postural development and movement patterns. Normal cognitive skills and motor maturation accommodate a person's inherent need to move and to use the body in recreation and play.

For the child with PWS, the phenotypic body shape that became evident in childhood remains throughout adolescence and adulthood. Without growth hormone intervention, the lack of a prepubertal growth spurt along with the failure to fully develop secondary sex characteristics (e.g., waist and hip body form) serve to amplify the already present impact of hypotonia and insufficient lean muscle mass. Thus, in comparison peers, the child with PWS who does not receive GH treatment will be short, particularly when compared with grown family members, and will have small hands and feet. The average height of adults with Prader-Willi syndrome is below the fifth percentile [10]. As previously indicated, GH treatment generally normalizes height as well as the size of hands and feet.

Further, by adolescence, even with continuing GH treatment, without rigid dietary adherence, continuing growth of body fat may result in total body fat of 40–50%. The excessive body fat is most likely to accumulate at the body's midsection and thighs [18, 19]. The combination of low tone, postural muscle weakness, high center of gravity, and excessive body fat ensures that posture will fall outside of normal plumb line alignment, preventing postural stability, normal gait, and movement patterns. Inactivity is often the result of the affected teenager's body shape and physical status. Cognitive and oppositional behavioral tendencies are additional factors impacting these teens' and adults' potential for improving body size and shape.

Sensory Integration

In addition to developmental neuromotor delays and differences, children with Prader-Willi syndrome typically present with sensory integration deficiencies. Sensory integration refers to the brain's ability to organize the information received from all the body's sensory modalities—vision, hearing, touch, taste, position in space, pull of gravity, and movement [20]. When development is typical, children receive and organize sensory input to produce well-coordinated movement, behavior, and self-image. For the child with Prader-Willi syndrome, poor muscle tone and short stature are just two of the many factors that impact successful sensory integration. The value of a sensory integration evaluation and sensory integration remediation program cannot be over emphasized. From the first 12 months and throughout development, sensory integration therapy can impact feeding, gross and fine motor skills, language development, behavior, and cognition. Physical therapists, occupational therapists, and speech therapists will all incorporate sensory integration strategies into their therapy treatment plans.

Gait From childhood and into adulthood, persons in the Prader-Willi population often demonstrate gait patterns which are distinctive—even as compared with obese control groups [21]. The gait anomalies are directly related to the hypotonia, low muscle mass, and obesity which distributes the fat to the thighs, buttocks, and abdomen. The distribution of the body fat, the gluteal and core weakness, and the low tone result in characteristic anterior pelvic tilt and postural instability and malalignment. While all children's posture features anterior pelvic tilt at defined phases of skeletal development, the child with PWS does not develop the strength or tone to align the pelvis posteriorly by the expected 10–11 years of age. The persistence of the anterior pelvic tilt invites shortness across the hip flexors which then ensures hip flexion through the entire gait sequence.

Studies of gait analysis of the Prader-Willi population (teens and adults) reveal several other consistent findings. The pace of gait tends to be slower with shorter stride lengths and longer stance phases. Push off at terminal stance is decreased in power and efficiency as a result of hypotonia and plantar flexors which are not strong enough to propel the body weight against gravity and through space. The knees tend to be flexed instead of fully extended at terminal swing phase—just before the foot hits the ground to begin a new stance phase [22].

Normal symmetrical gait is very energy efficient. The gait of a person with Prader-Willi syndrome is very energy consuming. Therapy

programs which encourage activity as low impact as walking can yield improvements in strength and muscle mass for children and adults with PWS. It is suggested that therapy programs in early childhood have the potential to prevent and minimize the evolution of faulty gait patterns [23]. The impact, if any, of GH treatment on gait has not been studied.

Orthotics Ligamentous laxity often accompanies the hypotonicity of Prader-Willi syndrome. Ligaments which are too loose cannot hold the many joints of the feet and ankles in normal alignment. Malalignment through the feet and ankles prevents optimum recruitment of existing strength. Inability to recruit maximum muscular power increases energy expenditure and results in impaired performance and fatigue. Lax ligaments cannot be made taut, but the ligamentous laxity at the feet and ankles can be addressed. When ligaments are not able to support the bony structures of the foot throughout growth, orthotics should be utilized. Orthotics are tools to provide proper alignment, to prevent deformity, and to promote proper foot and ankle function. While orthotics are most commonly designed to support the structures of the feet and ankles, the support provided at the feet and ankles will positively impact the alignment at the knees and hips.

Firm, supportive foot wear with a small arch support is beneficial for all early walkers who exhibit low tone and ligamentous laxity, and a resulting weight-bearing pattern is described as flexible flatfoot. By age 3, more specific orthotic management can be pursued for children exhibiting low tone and ligamentous compromise [24]. With 28 bones in the foot and 55 articulations, there can be no one-size-fits-all recommendation for orthotic prescription. A child with Prader-Willi is well served by a clinical team which includes an orthopedic physician, a physical therapist, and an orthotist to carefully evaluate joint and postural alignment from the tip of the toes to the trunk.

The specifics of an individual child's orthotic needs are exceedingly variable, and the orthotic prescription will vary with growth and developmental stages. To accommodate growth, orthotics might require replacement within 9–12 months. However, changes in anatomy and function could necessitate orthotic modification even more frequently [25].

Patellofemoral Syndrome Patellofemoral syndrome is a common cause of knee pain that is grossly underreported in all teens. Even when musculoskeletal development and lean body mass are within normal limits, muscle and soft tissue imbalances at the hip and knee are a frequent cause of patellofemoral knee pain. The hypotonia and typical body shape render the teen and young adult with PWS even more susceptible to this very common cause of knee pain. Patellofemoral syndrome results when the patella, or kneecap, does not track accurately through the patellar groove during flexion and extension movements. The faulty tracking occurs as a result of a variety of musculoskeletal factors.

Of the four quadriceps muscles, the lateral quadriceps (vastus lateralis) is the strongest and most likely to pull the kneecap laterally (to the side), away from the appropriate pull path. The medial quadriceps (the vastus medialis oblique), which should activate to pull the kneecap medially (to the middle), is the smallest and least powerful of the quadriceps. Most commonly in those with PWS, the exaggerated anterior pelvic tilt keeps the femurs internally rotated, further preventing the activation of the vastus medialis oblique.

The gluteus medius muscles located at the lateral aspect of the hips are important pelvic stabilizers. Even in the normotonic population, the gluteus medius musculature is frequently too weak to prevent dropping of the pelvis, which contributes further to patellar malalignment. Gluteal weakness, as well as hyperextension of the knees (genu recurvatum), is a common postural characteristic among those with PWS. Genu recurvatum contributes to patellofemoral dysfunction because the knee rests in extension without benefit of any quad muscle input. Furthermore, knee hyperextension, or recurvatum, occurs with the femur fully internally rotated.

Patellofemoral pain occurs when bending or straightening the knee. Those troubled with patellofemoral syndrome will experience pain when ascending and descending stairs, and will frequently describe knee pain upon rising after extended periods of sitting. The most dramatic sequela (long-term outcome) of patellofemoral dysfunction is subluxation, or dislocation, of the kneecap. Patella dislocation typically has a sudden onset, often with no identifiable precipitating event. If patellar relocation (return to normal place or position) does not happen spontaneously, it can easily be put back in place in the emergency department. Immobilization in a splint or cast offers rest and an opportunity for swelling to subside.

Preventing repeat patellar subluxations (dislocations) is of paramount importance. While surgical stabilization is one treatment option, a strengthening program for the medial quadriceps and gluteus medius musculature, combined with a stretching program for the iliotibial and of the lateral thigh and hamstring muscles and a patellofemoral taping program [26] offers a conservative approach that can successfully rehabilitate the knee and prevent the need for surgical intervention. Patellofemoral reeducation has a high rate of success in the normotonic population and offers a reasonably conservative option for members of the Prader-Willi population who are cognitively able to understand and execute the exercises, and who have the support persons to ensure compliance with the program. The improvement in muscle strength and tone provided by GH treatment could potentially have a significant impact on the incidence and prevalence of patella-femoral syndrome; new data gathered over time from those who have been GH treated will be necessary to determine the impact of treatment on patella-femoral syndrome.

Scoliosis In the normotonic population, idiopathic (specific cause unknown) scoliosis occurs in 2–3% of children aged 7–16 years [27]. Those with Prader-Willi syndrome are more at risk for neuromuscular scoliosis, presumably as a result of low muscle tone. Approximately 62–68% of the Prader-Willi population have scoliosis with a structural change of at least 10° [28, 29]. The high prevalence of neuromuscular scoliosis among children and teens with PWS necessitates careful monitoring by radiographic studies, especially during periods of rapid growth. Progressive curves (curves that have increased by 5 or more degrees on two consecutive examinations) should be evaluated radiographically every 4–6 months. The treatment of neuromuscular scoliosis ranges from careful monitoring to bracing to surgical stabilization. The presence of scholiosis is not a deterrent to GH treatment but requires that any scholiosis process receive extremely careful and frequent monitoring during the growth years, especially as that growth is aided by GH treatment.

Inactivity and Obesity

The school-age child with Prader-Willi syndrome will most likely be active and playful with school peers. However, the child most likely will be unable to compete or even maintain pace with peers. Standardized testing reveals objective data for better understanding the motor difficulties encountered by school-age children with PWS. The Bruininks-Oseretsky Test of Motor Proficiency is a standardized assessment for children aged 4–14 years [30] that defines specific areas of weakness: muscle strength, speed, balance, coordination, and bilateral skills.

The genetically driven hypotonia, weak musculature, and higher fat-to-lean body mass ratio lead to motor delays, reduced spontaneous physical activity [10] and frank inability to acquire the needed skills for developing strong and lean bodies. Even when GH treatment improves muscle strength and tone, and helps maintain a more normal fat-to-lean body mass ratio, there usually remains a discrepancy between the motor capacities of someone with PWS and their age-matched peers. Rarely do organized and intramural sports make a place on the team for a child with Prader-Willi syndrome, independent of GH treatment status.

The physical therapist working with the school-age child with Prader-Willi syndrome

must address these issues of inactivity and impending or existing obesity. While the children are still in school, adaptive physical education programs can be invaluable for maintaining an activity level and increasing strength, muscle tone, and aerobic capacity. Modified track, swimming and water play, tricycles and bicycles—adapted as necessary—and all forms of gym and playground play can be fun, therapeutic, and safe.

Special Olympics programs and local disabilities sports leagues designed for individuals with disabilities also are a wonderful option for families of a child with Prader-Willi syndrome. These programs can provide the means and motivation for dealing with weight, weakness, and inactivity through organized and supportive sports and play. Beyond the physical benefits, these programs offer affected children the joy of movement and play, the thrill of competition, and the comradeship of a team, which might otherwise be unavailable for this population.

The Adult with Prader-Willi Syndrome

The U.S. Food and Drug Administration (FDA) approved growth hormone treatment for children with Prader-Willi syndrome in the year 2000. Growth hormone is changing the future for Prader-Willi children. Adults with Prader-Willi syndrome—especially those adults who were born too soon to benefit from growth hormone therapy—face challenges that follow them from childhood and other challenges that emerge in adulthood.

The postural instability that first emerged in childhood often becomes more problematic in adulthood. The persistent ramifications of hypotonia, small stature, a high center of gravity, increased body weight, decreased opportunities for physical activities in the post-school-age population, and gravity all conspire against proper upright plumb-line postural alignment. Simple techniques can curb the forward flexed posture that so often typifies the adult with PWS.

Time spent each day in the prone or tummy-lying position with weight propped on forearms strengthens the back extensors and shoulders and stretches the flexors of the trunk and hips. Upper extremity and upper body strengthening programs can modify the stereotypic head-forward and shoulders-rounded posture. Such upper body strengthening and stretching programs might include swimming, wand exercises for the shoulders, pulley exercises, range-of-motion exercises done with resistive bands, or even cuff weights starting at 1/2 pound and increased in 1/2-pound increments.

Adults with PWS are also at increased risk for osteoporosis and related bone fractures (see Chap. 5). Physical therapy and exercise programming should be carefully coordinated with medical monitoring and treatment for affected individuals. Walking, running, horseback riding, and jumping may not be optimal activities for a person with osteoporosis, since these activities may further increase the risk for fracture in the lumbar spine and hips (the major weight-bearing parts of the skeleton). Nonweight-bearing exercises, such as swimming and water aerobics, may be preferable. However, if a person is being medically treated for osteoporosis (e.g., with estrogens or bisphosphonate) and there is a documented improvement in bone density, then weight-bearing exercises can be judiciously reintroduced into the exercise regimen after consultation with the treating physician.

In the absence of osteoporosis, a walking program is an excellent weight-bearing activity for adults with PWS and very adequately stresses the long bones, facilitating calcium fill. It also provides a manageable aerobic exercise program. Walking is easily executed by people of all skill levels and requires no special equipment other than a pair of supportive shoes. When walking outdoors is impossible, the use of a treadmill can be considered. However, balance issues make this difficult for many with the syndrome, so this should not be attempted without proper supervision and attention to safety.

The need for aerobic activity does not decrease as the person with PWS reaches adulthood. Many

adults with PWS are predisposed by obesity to sleep apnea and hypoventilation syndromes. Aerobic activity offers the best defense against obesity and the best means of strengthening lung capacity.

Adults typically have fewer opportunities than children for organized physical activities, and this is particularly true for adults with physical challenges. As previously indicated, Special Olympics and other similar programs are invaluable in fostering motivation for physical activity and providing opportunities for organized, varied motor challenges.

Across the nation in large urban areas as well as in small rural locales, communities are building centers for fitness and education. These community centers are rising to the challenges of the nation's increased need for physical activity. These centers offer opportunities for all ages and skill levels to enjoy water play, court sports, and organized group exercise. Many of these wellness and fitness centers provide opportunities for those with special needs to utilize their facility.

Conclusion

Since 1956, when Swiss physicians Prader, Labhart, and Willi first described Prader-Willi syndrome, much has improved for affected children and adults. An increasing knowledge base and exciting treatment options, such as growth hormone, offer increased optimism for quality of life. At all stages of development, and throughout the life span of the person with Prader-Willi syndrome, motor intervention and activity modalities provide the tools for dealing with the challenges of hypotonia, developmental delays, balance instabilities, orthopedic anomalies, and obesity. From the infant, who has perhaps not yet even been diagnosed, to the adult seeking meaningful work through vocational training, every individual with Prader-Willi syndrome should have care that includes physical, occupational, and speech therapists as essential team members.

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11 Educational Considerations for Children with Prader-Willi Syndrome

Stacy Ward and Evan Farrar

US Education Legislation

Children with Prader-Willi syndrome (PWS) present unique characteristics, needs, and challenges to traditional educational environments. With rare exception, individuals with PWS will require special education and related services during their educational career. Providing an optimal education experience requires that parents, educators, related service providers, and administrators be familiar with the unique and complex issues affecting the student with PWS so that they may better meet the educational needs of that student. Further, parents need to understand the current federal laws that define, support, and guide school personnel in the provision of special education services. Current legislation has evolved from the original federal special education law "The Education of All Handicapped Children Act" that was enacted in 1975. The original law has subsequently been amended, renamed, and reauthorized multiple times leading us to the current statute titled the *"Individuals with Disabilities Education Act of 2004" (IDEA)*. IDEA has two primary purposes: first to provide an education that meets a child's unique needs and prepares the child for further education, employment, and independent living; and second, to protect the rights of children with disabilities and their parents [1].

The No Child Left Behind Act of 2001 (NCLB) was intended to ensure that all children have a fair, equal, and significant opportunity to obtain a high-quality education and reach, at a minimum, proficiency on challenging state academic achievement standards and state academic assessments [2]. With the reauthorization of IDEA 2004, Congress established consistency and agreement with NCLB. IDEA requires local education agencies (LEA) to use "proven methods of teaching and learning" based on "replicable research" while NCLB requires LEAs to implement evidenced-based methods of teaching.

IDEA is divided into five parts: Part A – General Provisions, Part B – Assistance for Education of All Children with Disabilities, Part C – Infants and Toddlers with Disabilities, Part D – National Activities to Improve Education of Children with Disabilities, and Part E – National Center for Special Education Research. Parents,

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special education advocates, and attorneys, as well as educators, will refer most often to Parts A and B.

IDEA Part A, Section 1401, includes 36 legal definitions that are key to understanding the intended protections of the law. In Section 1401, the definition of a *Child with a Disability* is quite lengthy; however, it outlines that a disability diagnosis alone does not meet the criteria under IDEA. The child must have a disability *and* because of that disability need special education and related services. Students with PWS, must meet both criteria to be eligible for a free, appropriate public education (FAPE) under IDEA. If a child has a disability and does not need special education and related services, they may be eligible for protections under Section 504 of the Rehabilitation Act.

Part B of IDEA focuses on children between ages 3 and 21. Section 1412 is a key statute that covers free appropriate public education (FAPE), Child Find, least restrictive environment (LRE), inclusion, and mainstreaming. Child Find outlines the school district's responsibility to identify, locate, and evaluate all children with disabilities, including those who are homeschooled, homeless, educated in private schools, and wards of the state [3]. States must ensure that they have policies and procedures in place to provide all students with disabilities FAPE in the LRE (with non-disabled children to the maximum extent appropriate), including those who have been suspended or expelled from school [4]. Further, students must have access to the general education curriculum, rather than being educated with significantly different content and programming.

Part C of IDEA focuses on early intervention services for infants and toddlers. An infant or toddler with a disability is defined as an individual under the age of 3 who needs early intervention services because they are experiencing developmental delays, as measured by appropriate diagnostic instruments and procedures in one or more areas of development [5]. States have the authority to include in that definition, "at risk infants and toddlers." Individuals who meet this definition are eligible for early intervention services that must be designed to meet their developmental needs, including physical, cognitive, communication, social, emotional, and adaptive needs. Part C further states that these services are provided by qualified personnel at no cost to the family except where Federal or State law provides for a system of payments by families, including a schedule of siding fees. In most circumstances, services are provided at no cost to the family [6]. Early intervention services must be outlined in an Individualized Family Service Plan (IFSP) that includes measurable goals and expected outcomes achieved [7].

It is necessary for all families engaging in the educational planning for their child with PWS to familiarize themselves with the latest provisions of the federal education laws. Several excellent resources include the US Department of Education (www.ed.gov), the National Dissemination Center for Children with Disabilities (www.nichcy.org), and Wrightslaw (www.wrightslaw.com). Additionally, obtaining state specific laws, policies, and procedures will better enable parents to secure a comprehensive and appropriate education for their child.

Qualifying for Special Education Services

As indicated, to be eligible for special education services under IDEA, a child must have a disability that interferes with their ability to learn, and by reason thereof, needs special education and related services. Thus, having a diagnosis of PWS alone does not qualify the child for special education services. Rather it must be further demonstrated that having PWS impacts and interferes with the child's ability to learn. In order to document special learning needs, the law requires that school districts evaluate children with a disability or suspected disability by an interdisciplinary team using several different evaluation tools. This includes information and evaluations provided by the parents [8]. Once a child is determined eligible for special education and/or related services, a team comprised of general and special education professionals, school

administrative personnel, the child, parents, and others who have specialized knowledge of the child will develop an Individualized Education Program (IEP).

An IEP must include a statement of annual achievement goals that address the student's present level academic achievement and functional performance, including how the student's disability affects their involvement and performance in the general education curriculum [9]. While there are some symptoms that all students with PWS share in common, such as hyperphagia, which interferes with the student's ability to focus and learn when food is visible or present, Prader-Willi syndrome affects each child's ability to access the curriculum differently; thus, it is important to document the information discovered in comprehensive evaluations in the present level of performance section of the IEP. All IEPs must also include measurable annual goals that address the present level of performance. Additionally, the IEP must include a statement of the related services, supplemental aids and services, and program modifications that will be provided, based on evidence-based research.

Program Models

There are variations in classroom options for preschool and school-age children with PWS. Which option is best depends on both the needs of the child and the support services the school system can provide in regular and specialized settings. Because all children's needs change overtime, including those with PWS, planning and placements require periodic review and often modification. Any model must incorporate understanding and support for the student's educational, emotional, and social development while "normalizing" all experiences as much as possible, and optimizing quality of life.

Although terms may be defined differently from state to state, most school districts recognize several program models. An "inclusion model" involves placing a child with disabilities such as PWS in the general education setting while providing individualized accommodations and support as needed. Where its interpretation is flexible and a broad array of educational and behavioral supports is available, it can be very effective. One advantage to this model is that all children are included and theoretically valued regardless of ability or capacity. The classroom environment is altered to accommodate all students' needs. Another advantage is that children can develop friendships with classmates with whom they might not have otherwise interacted.

In the inclusion model, related services such as occupational, physical, and speech therapy can be incorporated into the general education classroom or take place outside of the classroom. Some students may benefit from having a PWS-trained paraprofessional, or a one-to-one aide provide needed educational, behavioral, and social support throughout the school day, and specifically when food is obtainable. For students with PWS, this model also must incorporate support services to be employed when difficulties arise; however, it is clearly preferable that prophylactic supports are established to manage anxiety and its resultant behavioral manifestations. For example, psychosocial/behavioral consultation to establish preventive supports may be beneficial in situations such as managing food security concerns, frustration, transition, and the development of social skills and friendships.

When the inclusion model is not appropriate for a student, other models may be pursued. For students with more complex learning or behavior challenges for whom the inclusion model requires attendance in schools with large classes and few supports, a smaller, specialized class for academic work may beneficial. However, classrooms for children with emotional disturbances (often termed "ED classrooms") typically are not the appropriate setting for students with PWS, as the etiology of behaviors is quite different from those typically classified as ED. When specific behavior management strategies need to be implemented, a functional behavior assessment should be completed by a behavior analyst or school psychologist with PWS experience and behavior analysis training.

Regardless of the classroom model, benefits to socio-emotional development can accrue from

integrated experiences. Integration into a class of general education students for structured activities such as music, science, or art projects can be successful; however, activities that involve food such as lunch or snacks may pose specific challenges for the student with PWS and will likely require one-to-one supervision and support. Classes such as those that involve cooking and visits to a mall food court, typical in many high school Transition Programs, are likely inappropriate for the student with PWS and certainly should not be attempted without the accompaniment and protection of a 1:1 aide.

A small percentage of students who exhibit significant behavioral instability may benefit from placement at a residential school where a predictable structure, a high staff-student ratio, and limited access to food create an environment that greatly reduces anxiety and anxiety-related behaviors. This model can be very effective when the residential school is well versed in educating students with PWS. Parents remain an integral part of the IEP team and should remain in close communication and cooperation with the program to ensure an appropriate educational experience for their child.

Regardless of the educational model selected by the IEP team, teachers and all other school personnel working with the student with PWS must be educated about the need for food security, typical and student-specific behavior challenges, and social deficits that the student with PWS experiences. It is equally important that educators are taught to recognize the strengths of their student with PWS, for the success of all, teachers must be taught how to gear their teaching strategies toward the student's strengths.

Medical Issues That Affect the Educational Process

There are several medical and psychological components of PWS that educators need to be aware of, particularly an altered level of arousal, narcolepsy/cataplexy, hyperphagia, diminished muscle tone, and motor planning skills. These features impact both academic performance and the perceptions of the student by school personnel and classmates.

Children with PWS frequently demonstrate a diminished sense of arousal and may have a secondary diagnosis of narcolepsy or cataplexy. While some children with other medical conditions can be excessively active, most children with PWS are underactive. This characteristic manifests itself as a decreased initiation of activities, and a frequent lack of enthusiasm. For example, some children tend to fall asleep when participating in sedentary lessons such as listening to a lecture or silent reading. This is often misinterpreted as an inability or unwillingness to participate, when it is in fact an altered level of arousal mediated by the central nervous system and is unrelated to intelligence or desire to learn.

Hyperphagia, an abnormal excessive drive to eat or obtain food despite the quantity of food consumed, is often the most disabling symptom of PWS. Unlike arousal, the appetite is excessive rather than diminished. While mild in some, hyperphagia is profound in others; regardless of degree of food drive, everyone with PWS requires supervision when food is obtainable. Hyperphagia results from a dysfunction of the hypothalamus; it is a biological process that over-rides any willful control of the affected individual. The inability to control the drive for food is not related to cognition, disruptions in the home environment, or a need for emotional or physical nourishment. Children with PWS cannot control their appetite and it is imperative that the environment is modified to limit access to unauthorized food and prevent food seeking behaviors.

Another feature of PWS is hypotonia (low muscle tone) and diminished ability to successfully engage in tasks requiring substantial motor planning skills. Growth hormone medication, now considered standard of care in children with PWS, improves but does not normalize muscle tone. Therefore, despite the use of growth hormone, children with PWS continue to be weaker and motor tasks such as dressing are often difficult, regardless of cognition. Students may fatigue quickly after participating in physical education or therapy sessions that require a lot of fine or gross motor activity; therefore, careful

consideration should be given to the placement of these classes in the student's schedule so they do not overly fatigue the student and therefore interfere in the student's subsequent learning activities or increase maladaptive behaviors.

Educational Concerns Across Developmental Stages

Infancy and Toddlerhood (Birth to 3 Years) The infant and toddler years are rapid periods of development and learning, for all children, including those with PWS. A strong social orientation as an infant is a vital strength upon which to build a successful learning and intervention program. *IDEA Part C* was updated in 2008 to include language about the need "to recognize the significant brain development that occurs during a child's first 3 years of life" and the need "to maximize the potential for individuals with disabilities to live independently in society." As early as possible, within the first few weeks of life if possible, early intervention services should begin.

Infants should be assessed for feeding and oral motor skills, gross and fine motor development, and receptive and expressive language achievements. Once assessed, any delays should be addressed through therapies that are focused on improved feeding, physical stimulation, improved motor development, and motor planning skills including sensory integration, communication, and socialization. Assessments should be ongoing and periodic. Singing, nursery rhymes, reading, mirror play, bubbles, pictures, "rough" play, and cuddling are all vital developmental activities that infants with PWS should be exposed to with adjustments to compensate for motor and speech limitations. For example, providing more physical support, exaggerating affect and facial expressions, and reinforcing all vocalizations and other attempts to communicate may be needed to overcome arousal and attention deficits.

During the early years, due to output delays in the motor and speech systems, cognitive processes tend to develop ahead of physical skills. The capacity for thinking and understanding generally precede verbal expression. Expressive language generally lags receptive language which tends to correlate highly with cognitive development. The cause of this initial speech delay is due, in part, to oral motor difficulty. The delay frequently causes frustration for both the child and their speaking partner. Further, limited expressive and motor skills make developmental assessment difficult and may result in underestimation of cognitive abilities. Using multiple assessment tools will help mitigate this risk.

Referral to Early Intervention services should be initiated immediately following diagnosis, often while still in the NICU. In some states, services are provided through the Department of Education, while in others they are provided by the Department of Disability Services (or similar title). These specialized early interventions should be taught and incorporated into daily and weekly routines that encourage optimal adaptation over time. In addition to specialized early intervention services, infants and toddlers with PWS typically benefit from playgroups or day care settings that provide rich opportunities for enhancing social communication and play skills.

Preschool (3–5 Years) Toddlers, with or without PWS, begin to exert their independence as they progress through the developmental milestones of walking and talking. Individual personalities emerge as they learn to express themselves, make demands, and struggle to gain control of their environment. Interests, needs, and preferences may be expressed with great conviction and adults may be met with opposition. During this developmental period, children know what they want, and when they want it. When gratification is not immediate, frustration can turn into a tantrum, especially when verbal expression is limited. Who has not heard of the "terrible twos" or "threenagers"? For children with PWS, this phase may begin a little later and last a little longer.

Although preschool children with PWS may exhibit delayed motor or speech abilities, they too crave their independence. Delays in achiev-

ing these milestones can contribute to resistance to physical activities, frustration due to their lack of physical ability or inability to communicate, and result in tantrum behaviors. Difficulty with transitions, inconsistent compliance, and emotional dysregulation may occur; tantrums may be frequent and intense during this stage. Implementing positive behavior strategies and speech and physical therapies, as well as creating a predictable environment, are essential.

At the age of 3, children may become eligible for special education and related services through the public education system, based on assessment and evaluation. Cognitive, communicative, social, physical, and behavior skills are assessed in order guide academic approaches, develop goals, and determine placement. In addition to including complete transitional summaries and recommendations from a child's early intervention program, supplying the school team with educational information about how PWS symptoms impact the child is critical.

Developing the IEP involves the administration of standardized intelligence tests. Interpreting the test results requires an awareness of the broad spectrum and characteristic patterns of learning difficulties in children with PWS. Most children with PWS function in the mild range of intellectual disability, while a small percentage are severely impaired. Regardless of IQ scores, children with PWS show substantial variability across domains.

Children with PWS who need specific educational support may benefit from a specialized preschool experience, such as an integrated, special needs, or language-based classroom. Others with fewer needs may benefit from enrollment in a general education preschool where, although less individualized support may be provided, there are increased opportunities for socialization and group experiences. A common successful approach is enrollment in a combination of special and general education programming, or in an integrated program that includes some children without special needs. Regardless of ability, most children with PWS can manage attending two programs if approaches and daily activities remain consistent.

Preschool IEPs, in addition to present levels of performance and goals, should include a preacademic curriculum in a developmentally appropriate context. Most children will continue to benefit from speech, physical, and occupational therapies while in preschool. These services are most effective when the therapist spends a portion of their time in individual and/or small group sessions and some time consulting with the classroom teacher on how to incorporate therapy goals into the curriculum and classroom activities. Preschoolers with PWS sometimes engage in behaviors that result in class disruption including impulsively blurting out answers, difficulty waiting and turn-taking, difficulty managing personal physical boundaries, and refusal behaviors; these behaviors also can interfere with learning and acceptance by their peers. These behaviors should be analyzed through a functional behavior assessment (FBA) and addressed in a positive behavior intervention plan (PBIP) that is attached to the IEP.

At this age, children with PWS not only realize that eating is unrestricted for their peers, they also note that others' food may be accessible. Several strategies can help manage this situation. During school hours, edibles should be kept outside of the classroom in cubbies or in high cabinets out of sight. If food is available or believed to be available, the student typically focuses on how he or she can obtain that food and cannot focus on the task at hand. If snacks are served in the classroom, they should be served in single portions, placed in front of each child then put away out of site. Supervision is necessary whenever food is available. Food should not be used in classroom activities, used as rewards, and preferably should not be kept in the classroom at all. Matters regarding food are a constant concern that require teachers, aides, and families to communicate closely and function as a team. When teachers are aware of potential difficulties, the environment can be structured to minimize problems and facilitate success.

School-Age Children (6–12 Years) Developmental goals of school-age children include mastery of tasks and learning to take pride in their

achievements; developing a desire to acquire knowledge and skills; and mastery of their environment. Providing the student with PWS many opportunities for success is vital to the development of a healthy self-esteem during this period when awareness of differences emerge. Some children will engage in tantrums and skin picking during this period in response to increased anxiety and decreased frustration tolerance. Social development continues, as do social challenges, especially the development of friendships.

During this developmental period, feeling successful with some physical activity is important in shaping lifelong attitudes toward exercise. Participation in both school activities and outside programs, such as Special Olympics, can be very rewarding both personally and socially. Noncompetitive activities, such as swimming, walking, and group exercise classes, are good alternatives to team sports.

Younger students with PWS often do well in general education classrooms when provided with the support and services they need. Meticulous attention must be given to the learning profile of the student with PWS as they begin their school career. Their learning profiles, although unique, often have characteristic strengths and weaknesses. Strengths, indicated in Table 11.1, are relative to their own abilities, not peer performance. Many students with PWS have excellent long-term memory skills. This strength applies to academics as well as events and names. While it may initially be more difficult to teach new material, once learned, it is learned forever. Functional skills should be encouraged early in the curriculum using positive reinforcement, such as praise, individualized attention, and preferred reinforcers.

Many children with PWS become skilled readers. Verbal information is best comprehended when presented in brief pieces with time allowed for processing before moving to the next piece of information. Learning through hands-on experiences is often a successful approach. Visual materials, such as photos, illustrations, and videos, are useful teaching aids, as visually based learning is a strength for many students with PWS.

Learning difficulties often present in children with PWS in distinct areas, as shown in Table 11.2. One area of relative weakness is short-term auditory memory, making it difficult to remember verbally presented information. When multi-step directives or a list of steps/objects is presented, the demand for understanding and response is compounded by limited expressive language ability. It may be that children have difficulty transferring auditory information from short-term to long-term memory. However, when given the opportunity to learn through repetition and attaching meaning, information can be recalled from long-term memory. Difficulty remembering strings of verbally presented information can be misinterpreted as noncompliance, rather than the child's inability to sequentially process multiple step directives. Performance can improve through repetition, repeating directions, writing down procedures, using visual aids, and modifying verbal instructions. A speech therapist can be helpful in working with the child as well as with classroom staff to teach these strategies.

Fine motor skills and motor planning tasks, such as writing, drawing, and cutting, also present as relative difficulties, although a few children are particularly good in this area. Most can improve over time and with practice. Computer usage should be incorporated into the classroom as early as kindergarten. Minimizing writing demands, providing alternative assignments (either color a picture of a train or find one in a magazine), as well as facilitating opportunities to

Table 11.1 Characteristic learning strengths

Long-term memory information
Receptive language
Hands-on experiences/learning
Reading

Table 11.2 Characteristic learning weaknesses

Expressive language
Short-term auditory memory
Fine motor skills, related to strength, tone, and motor planning
Interpreting social cues, learning subtle social norms

practice new motor tasks can reduce find motor fatigue and frustration. Learning is more effective when the correct answer can be selected from a multiple-choice format rather than tracing or filling in the blanks.

Physical education and therapy are useful for developing strength, coordination, and balance as well motor planning skills. Gross motor activities such as walking, swimming, and low-impact aerobics are good choices for children with PWS. Physical education should enhance opportunities for socialization as well as foster regular, healthy exercise patterns.

While behavioral and social challenges discussed in the previous section also apply to school-age children, perseveration and obsessive behaviors may increase in both frequency and intensity. Perseverative questions are managed best by answering the question no more than three times, with the third including a written answer to which the teacher can thereafter direct the student.

Adolescence Adolescence is traditionally a challenging time for children, having to cope with increased pressures coming from multiple sources. For those with PWS, the growing awareness of the differences between themselves and their peers without PWS occurs at a time when "fitting in" is so important. Individuals with PWS who observe changes in their peers, but see fewer or no changes in themselves, are likely to experience increased distress. This distress may engender sadness, embarrassment, shame, and anger, and may result in resistance behaviors or food-seeking to salve the emotions, but it ultimately interferes with the individual's ability to learn and further impedes the ability to acquire and keep friendships.

Schools can benefit from annual consultation with a professional familiar with PWS. For some teenagers, specific behavior approaches such as behavior contracting can be effective in managing challenging behaviors, and can continue to be organized through a Behavior Intervention Plan (BIP). Tantruming, excessive skin picking, and behaviors that at first blush may appear as oppositional or defiant behaviors instead frequently reflect the individual's inability to cope with stressors and anxiety and need to be addressed promptly and comprehensively.

While challenges exist, there are also positive aspects of adolescence. Many teenagers develop effective verbal skills and become active participants and contributors to school activities. While it is generally difficult for people with PWS to cultivate friendships independently, satisfying relationships are possible. Due to behavioral and food-seeking challenges, most teenagers with PWS need continued and continuous supervision to keep them safe. Educationally, this is a time during which vocational planning and work experiences should be explored as part of transition planning and outlined in the IEP, while keeping the need for continuous supervision at the forefront of every discussion. School personnel must provide needed supervision during the school day, while parents must provide needed supervision at home, while at the same time all must cooperatively identify ways to increase the student's perceived sense of independence.

Graduation School districts have the authority and responsibility to establish the requirements for awarding a high school diploma. Members of the IEP team have the responsibility to determine whether the student with PWS is likely to be able to meet those requirements as well as what accommodations and services may be needed, or whether the student is better served by graduating with a certificate of completion or attendance or an occupational diploma. It is important to understand the diploma options offered in each school district and what they mean. These discussions should begin before the onset of high school, with IEP team members considering the student's academic aptitude as well as their ability to tolerate and manage stressors and anxiety. For the student who is diploma bound, it is critical to ensure that the curriculum, supports, and services reflected in the IEP do not jeopardize the requirements of a diploma. For example, *accommodations* made to support the student's learning do

not preclude obtaining a diploma, whereas *modifications* to the curriculum typically prevent that student from receiving a diploma.

Students who graduate from high school with a diploma are no longer eligible to attend a publicly funded school. There are some students with PWS who attend community college; however, new supervisory supports must be implemented because post-secondary education is no longer governed by an IEP but rather by the Americans with Disabilities Act. Some states delay a disabled student who graduated with a diploma from accessing services until they reach the age of 22.

Students who graduate with a certificate of completion or attendance are eligible to remain in high school until they reach the age of 22 (one state's age limit is age 26); however, most colleges and technical schools do not accept a certificate of completion or attendance or an "Occupational Diploma."

Whether receiving with a diploma or a certificate, at the time of graduation, the school must provide the student with a summary of academic achievement and functional performance that is based on that student's unique needs and post-secondary goals. Parents and educators should consider what supports the student with PWS will need to prepare them for their future, whether it is post-secondary education, employment, or supported living, keeping in mind that the level of support will look different for each student based on their strengths and challenges.

Conclusion

Students with PWS can achieve success in the school setting when parents and educators work together as equal members of the IEP team. The success of the student with PWS is significantly increased when educators recognize and accommodate to the individual student's unique strengths and challenges, as well as provide the necessary supports and services that are required by the PWS diagnosis.

References

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5. 20 U.S.C. §1435.
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12 Tools for Psychological and Behavioral Management with Prader-Willi Syndrome

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Chapter Overview

Prader-Willi syndrome (PWS) continues to unfold as one of the more complex and puzzling genetic syndromes. Most medical texts identify PWS primarily as an obesity syndrome, characterized by lifelong hyperphagia (the physiological drive to eat or obtain food despite the quantity of food consumed) with accompanying endocrine deficiencies, cognitive deficits, and behavior difficulties [1–5]. Without question, hyperphagia is a central driver of behavior [6, 7]; however, the documented range of intractable behaviors and neurocognitive deficits, coupled with neuroimaging studies [8–12], indicates that separate from the hyperphagia, Prader-Willi syndrome: (1) is a *pervasive* neurodevelopmental syndrome with a characteristic behavior profile that includes a risk for behavior disorders and psychiatric problems, and (2) reflects a distributed central nervous system dysfunction that has yet to be fully described either anatomically or biochemically. From this perspective, the centrally driven, food-related behavioral constellation, albeit dramatic, is just one aspect of the neurobehavioral profile attendant to this disorder and, when appropriately addressed, is perhaps the easiest of the behavioral abnormalities to manage.

Even among a population of individuals with genetically driven developmental disabilities, PWS is unique in its complexity and many frank contradictions [13]. Behaviorally, the young child with PWS is described as happy, personable, affectionate, cooperative, and compliant, despite the emerging hyperphagia. In direct contrast, however, by the time persons with PWS reaches adolescence, unless obesity is life-threatening, behavioral difficulties—often severe—become the central issue for individuals with the syndrome and their families [14–16]. Similar contradictions are apparent in day-to-day behavior functioning, and such contradictions are the challenge and complexity of the syndrome. For example, while affected individuals have reduced muscle mass and low muscle tone, they can display extraordinary strength when angry. Further, while most affected individuals assert and demand of others a rigid following of rules, by contrast there is a failure to recognize any contradiction when they themselves fib, lie, or cheat—especially when such behaviors involve acquiring food. Additionally, measured IQ scores range from profound intellectual disability to some individuals who test in a normal range and are also high academic achievers—yet these

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same individuals may be completely unable to determine weather-appropriate clothing or to cross a busy street safely. Similarly, the sweetest, kindest, most affectionate individual may (instantly) become verbally or even physically aggressive if feeling overwhelming frustration. Further, those who appear to manage themselves well with food today may steal food tomorrow if given the opportunity.

The presence and severity of behavior problems varies across individuals despite genetic subtype homogeneity and varies within a single individual across time. Nonetheless, all individuals with PWS display a typical food-related behavior profile that includes some degree of hyperphagia, and many aspects of this food-related constellation are manifestations of an underlying anxiety about food [17]. Similarly, most individuals with PWS have some degree of non-food-related anxiety that fuels or exacerbates various unwanted, maladaptive behaviors. Daily life fluctuations, hardly noticeable to someone without PWS, can be perceived by those affected as insurmountable overwhelming challenges, resulting in disruptive behavioral outbursts [18].

Cognitive deficits, executive function deficits, low frustration tolerance, low impulse control, and other neurobehavioral characteristics such as a tendency toward oppositionalism, inflexibility, and egocentrism play a significant role in the expression of maladaptive behaviors. Emotional instability may appear as depression, obsessions, and frank psychoses. Most persons with PWS are highly sensitive to the words we use, and their behavior is *extremely* dependent on their interactions or *perceived* interactions with individuals in their environment as well as on the structure of the environment. In many instances, these behaviors remain resistant to traditional behavioral and psychopharmacological management and can result in family turmoil and can present extraordinary challenges in obtaining safe community living and meaningful employment. Proven mental health interventions effective for reducing anxiety and depression, such as cognitive-behavioral therapy, are typically ineffective in individuals with PWS due to the lack of insight, self-awareness, and a high need to be "right." Further, care must be taken when seeking support from mandated reporters because of the propensity for individuals with the syndrome to confabulate and attempt to manipulate by making false allegations of abuse and/or neglect.

Despite the presence of these non-food-related behavioral features and their impact on the adjustment of affected individuals, there is a paucity of behavior management research on this population. With rare exception [19], behavioral research is descriptive in nature, directed toward determining the presence (or absence) of specific behaviors, skills, or abilities, and the differential impact of the causal genetic mechanism (chromosome 15 deletion vs. uniparental disomy) on these characteristics [20–23]. While critical for defining "typical" characteristics of affected individuals, these studies provide limited guidance regarding the day-to-day functioning of a specific individual and tend to underestimate the impact of environmental factors affecting behavior. In addition, many studies, in order to have a sufficiently large sample, include an age range encompassing infancy through middle to late adulthood, measured at a single point in time [24–26]. Such a methodology makes it difficult to assess age-related behavioral shifts.

Understanding PWS's most common physiological and neurological characteristics that can impact behavior will help inform and guide the care provider in the development of strategies and interventions to reduce anxiety thereby reducing the potential for unwanted and maladaptive behaviors. For even the most egregious behavior, there is *almost always* some precipitating event (trigger) or reason for the behavior that makes sense to the person with PWS, even if it is reported to come "out of nowhere." A key strategy is to determine the affected individual's logic behind the behavior, even if the reason does not make logical sense to the listener. It cannot be overemphasized that the behavior of the individual with PWS is *inextricably intertwined with, and reactive to,* their environment. Therefore, strategies and interventions targeted to reduce or eliminate unwanted behaviors must be predicated on creating the appropriate environment and then

managing that environment throughout the individual's lifetime, rather than attempting to directly modify the individual's behavioral responses. This chapter will first detail typical behavioral characteristics associated with PWS (termed behavior phenotype), examine critical management issues, and finally will provide strategies for effective management.

As with any child, it is most beneficial to implement PWS-specific behavior management strategies as early in life as possible in order to establish anxiety-reducing routines, rules, and boundaries that become a safe and unquestioned part of the individual's everyday life. Working to change and improve behavior patterns later in life is possible; however, it is often far more difficult and met with far greater resistance. When implementing some behavior management strategies for the first time, especially in older individuals, behaviors can get *worse* before they get better. The interventions presented in this chapter are designed to provide the foundation for positive *long-term* changes. There are very few "quick fixes" when it comes to PWS behavior management strategies. Since hyperphagia remains a key physiologic driver of behavior concerns, we turn first to the issues of hyperphagia and the accompanying food-related behavior constellation.

Overview of Behavior Phenotype

Hyperphagia and the Accompanying Food-Related Constellation

Despite decades of research, the causal pathophysiology of hyperphagia and the resulting obesity in PWS remains unclear. As currently understood, the hyperphagia in PWS is the end result of a highly complex, dysfunctional appetite regulating system coupled with a severely blunted neurophysiologic experience of satiety [7, 31–35]. As currently understood, the hyperphagia results from a signaling defect, wherein the brain does not properly receive or process signals of being "full" (termed satiety) and thus functions as if the body is starving, driving the affected individual to continuously find and eat as much food as possible. At the same time, to further protect itself from starvation, the body lowers the metabolic rate to almost half that normally expected in order to conserve energy and stores excess food intake as available fuel in the form of fat. Unmanaged hyperphagia plus a slow metabolic rate causes rapid weight gain that can quickly result in morbid obesity and obesity-related complications that can lead to premature death. In addition to providing a "food safe environment" with proper dietary adherence and access restrictions, constant supervision also is required to prevent death from choking and to prevent binge eating which can lead to stomach or bowel perforation, gastric necrosis, and death [36]. While hyperphagia is always present in affected individuals, there is wide variability among individuals in the degree and severity of hyperphagia and food-seeking behavior, ranging anywhere from interest only in what others are eating, to simple "opportunistic" food acquisition, to constant foraging and physical aggression to obtain food (Table 12.1).

Personality/Behavior and the Development of Behavior and Emotional Difficulties Like their non-affected peers, individuals with PWS demonstrate a range of personality traits, talents, interests, strengths, and weaknesses [37–39]. In addition, the genetic alteration seen in this population may be *specifically* associated with a number of frequently challenging behavior and personality traits [40, 41]. These traits and characteristics (termed a behavioral phenotype), while common among most affected individuals (Table 12.2), may differ in severity between individuals, and may differ in severity in a single individual at different times.

In addition, empirical data support clinical observation and parents' reports of a sequence of distinct behavioral/personality "epochs" [42, 43]. As indicated, infants and young toddlers with PWS are usually described as cheerful, compliant, and cooperative. However, with the advent of emerging hyperphagia, several predictable behavioral shifts occur, shifts that are independent of intellectual, language, or motor capacity

Table 12.1 Overview of the food-related behavior constellation [27–30]

Behavior category	Observed behavior
Hyperphagia	Extreme and constant (over) eating
Preoccupation with food	Constant need to know when the next food will be available Detailed food-oriented questions: what that food might be, serving size, how will it be cooked An assurance that the food information provided is certain Hypervigilance for food via collection of restaurant advertisements, newspaper and magazine pictures and recipes, and other visual reminders of food
Food seeking/ foraging, sneaking, hiding, and hoarding	Taking from others' food trays at school Asking others to give them their food Looking for food in others' desks, lockers, purses, backpacks Foraging from leftover food plates, trays, and garbage cans Sneaking food from kitchen or pantry and hiding in room
Eating unusual food items	Sticks of butter Saved "used" grease Pet food Decaying or rotten food Food-flavored items such as shampoos
Maladaptive and sometimes illicit/ illegal behavior directed at obtaining food	Lying, such as untruthfully telling school personnel that the family failed to provide breakfast or lunch Shoplifting Surreptitiously "borrowing" money from parental wallets for later food purchase Purchasing food via the Internet
Low liquid intake	Most individuals refuse to drink plain water and may therefore be prone to dehydration

Table 12.2 Broad behavior phenotype

Behavior category	Observed behaviors
Cognition and executive functioning	Wide variability of intellectual functioning; most function in the mild to moderate range of intellectual disability Independent of IQ score, an overlay of learning disabilities, processing deficits, and executive function deficits lead most to function in the mildly impaired range Executive function deficits: concrete thinking; difficulty planning, organizing, and learning from experience; impulsive, acts before thinking; attention deficits
Cognitive and behavioral inflexibility	Insistence on sameness Oppositional, stubborn, uncooperative, and often openly disobedient Inability to handle even minor daily transitions or changes Willful, oppositional, argumentative Difficulty with uncertainty and ambiguity Decreased tolerance for, and overreactive to, frustration and stress
Social perception, cognitive deficits	Social immaturity Egocentric Inability to see the other's perspective Insistence on having own way regardless of environment or others affected Difficulty recognizing emotions in facial expressions Difficulty recognizing and adhering to ordinary social cues (turn-taking, personal space, appropriate touch) Difficulty being or perceived as being "wrong" or making a mistake Deficits in social attribution Problems detecting and interpreting social information
Ritualistic	Extraordinary insistence on sameness Gets upset or distressed over small changes in routine or environment "Getting stuck", for example, perseverative speech and routines Obsession with an idea or activity (or person) Collecting/hoarding non-food items

Table 12.2 (continued)

Behavior category	Observed behaviors
Subject to sudden, intense emotional, and behavioral dysregulation and aggression	Cries easily for no apparent reason, or over small upsets Mood changes rapidly for no apparent reason Verbal and/or physical aggression or abusive behavior Impulsivity; acts before thinking about potential consequences Severe temper tantrums, rages, overt expression of frustration, anger
Sensory/self-stimulating/ self-injurious	Sensory deficits leading to inability to experience volume-induced discomfort when overeating Under reacts to pain Lack of appropriate fever response Abnormal response to ambient temperature—refusal to remove warm clothing even in excessive heat or conversely the refusal to wear warm clothing even in cold weather Smells, tastes, or licks objects Skin and rectal picking, gouging other body parts

[44, 45]. The initial shift coincides with the emerging hyperphagia and includes increasing oppositional tendencies, stubbornness, rigidity, increasing noncompliance, escalation in both food-related and other temper tantrums, shorter tolerance for frustration, overreaction to frustration, and a lessened ability to "go with the flow." Youngsters exhibit increased difficulty with transitions, even from one activity to another, and develop special routines and rituals that are difficult to avoid or circumvent. For many, attentional deficits are also noted.

A second shift is noted around 8–9 years of age with an escalation of previous patterns and a significantly increased rigidity of behavior, including the following: tendency to "get stuck" on a thought or question (perseveration); further evidence of attentional deficits impacting academics and behavior; increased worrying about both real and imagined problems and emerging chronic anxiety; less response to redirection and increased tenuousness of emotional control, coupled with less benefit from "time out" and "calming" efforts; increased need for invariance with excessive reactivity to changes in structure and routine; and an increased deficit to age-matched peers in social skills [37, 46–48].

Finally, another shift is associated with the chronological onset of adolescence. The impact of chronic anxiety becomes clearly evident, and increased mood instability frequently is coupled with more outwardly directed expressions of frustration and anger. Immaturity, in the form of insistence on having one's way, regardless of the situation, the environment or others affected often leads to social and relationship problems. For many, there is a continuing increase in reactivity to real or imagined hurts and injustices, and for some, the emergence of frank emotional and thought disorders. These behavioral epochs occur in both males and females and appear to be independent of cognitive, language, or motor abilities and BMI (body mass index) [49–51].

Although behavior difficulties are ubiquitous among those with the syndrome, genetic subtype behavior differences are reported. Hoarding and overt expression of frustration, anger, and aggression are more common among those with a deletion, while autistic spectrum behaviors are more common among those with UPD. Among those with a deletion, males tend to exhibit greater externalizing behavioral severity than females, particularly in adolescence; however, as adults, some individuals with a deletion have been observed to evolve into a milder overall behavior picture, while neither gender differences nor age-related behavior modulation has been observed among those with UPD [22, 52–55].

Cognition While the characteristics of PWS include cognitive/intellectual impairments, primarily in the mild to moderate range, data document a wide range of intelligence scores among affected individuals. When the findings of a number of studies are pooled, the following percentages emerge: No Impairment, or Full Scale (FSIQ) IQ >70, 21%; Mild Cognitive Impairment, 47%; Moderate Cognitive Impairment, 32%; and

Severe to Profound Cognitive Impairment, 2%. Genetic subtype (deletion type I or type II, or uniparental disomy [UPD]) differences in intellectual functioning are reported, but results are inconsistent across studies. Some studies have found no subtype differences in FSIQ scores; however, several studies report a greater number of UPD subjects with normal IQ scores when compared to those with a deletion. Additionally, significant subtype differences have been reported for Verbal vs. Performance IQ scores with those with UPD showing higher Verbal IQ scores and those with a deletion showing higher Performance IQ scores. However, even when differences in subtype scores are statistically significant, in no study have those differences reached the level of one standard deviation for the test utilized; thus, it is not clear that statistical differences reflect any functional relevance [56–58].

Regardless of genetic subtype, tested IQ scores yield an inflated estimate of ultimate behavioral capabilities. A separate pattern of altered learning processes including attention difficulties, slower than average overall rate of processing speed, deficits in short-term memory, sequential processing deficits, and difficulties in understanding, processing, and using verbal language collectively further depresses academic performance, adaptive functioning, and overall adjustment. Speech and language studies document specific deficits in vocabulary, receptive and expressive language, language comprehension, pragmatic language, discourse and conversational skills, and shortened length of utterances (see Chap. 9). Mathematics also is problematic for many with PWS. Problems in short-term memory as well as learning tasks that are sequential in nature present challenges that are often insurmountable. By contrast, many show strengths and even extraordinary abilities in long-term memory, visuospatial processing, and simultaneous processing with a specific ability in word search puzzles and assembling jigsaw puzzles [59–63].

As a result of multiple learning and cognitive difficulties, most affected individuals remain extremely concrete, rigid, and rule-governed in their thinking, and fail to develop abstract thinking abilities and concepts. Collectively, these cognitive difficulties impact the overall ability to adapt and have a direct impact on daily behavior. For example, a slower-than-average "rate" of learning, processing, and responding is observed in persons with PWS across all levels of cognitive ability—particularly when responding to precise verbal demands. Thus, if asked a question and rushed to provide an answer, frequently the result is an observable increase in anxiety and frustration. If this happens several times in close succession, increased frustration may escalate to unwanted negative behavior [64, 65].

Further, persons with PWS—though frequently highly verbal—often have difficulty explaining their actions. Even when behaviors are reasonable, affected individuals are frequently unable to articulate an explanation, escalating their frustration and raising the risk for verbal or even physical aggression. Moreover, language-processing difficulties combined with slower processing may result in an individual grasping only the initial elements of a conversation or set of instructions while additional elements of the ongoing interaction are missed.

Sequential processing deficits add further complications [58, 66, 67]. Persons with sequential processing deficits have difficulty telling time and comprehending temporal order (days of the week, months of the year), have difficulty integrating elements into temporal or sequentially ordered groups, and have trouble following a schedule or sequence, such as difficulty remembering what to do and when to do it. An inability to figure out what needs to be done and the order in which it must be done—especially if the task is not part of the learned, daily, predictable routine—leads to a constant state of being overwhelmed and anxious, with an increased vulnerability to even minor stresses (e.g., being rushed to change from one task to another).

Social Perception and Behavior An inability for abstract thinking is reflected in poor social relationships. Behaviorally these deficits are reflected as social immaturity such as an insistence on having one's way regardless of the situation, the environment, or others affected. In

addition, studies document deficits in recognizing emotions in facial expressions, difficulty recognizing and adhering to ordinary social cues (e.g., turn taking, respecting personal space, touching appropriately), and deficits in social attribution and interpreting social information [68–72]. Persons with PWS may recognize only a limited number of emotions, perhaps as few as two to three emotions along a continuum from extremely happy to very sad. Limited recognition of their own as well as others' emotions, coupled with difficulty in understanding another's point of view [73] predictably leads to problems getting along with others. Those who understand the world only in terms of "I want" or "I don't want" have difficulty with the social conventions and reciprocal behavior necessary for relationships. Comparatively, these deficits exceed those expected for cognitive ability and are similar to those found in individuals diagnosed with autism spectrum disorder [74–77]. In sum, this combination of cognitive difficulties leads to difficulties with learning, getting along well with others, and maintaining meaningful social relationships.

Separate from the typical personality, developmental and cognitive issues that influence the behavior of those with PWS, there are a number of known physical symptoms that, if present, may also influence behavior. These include the following: hypotonia and motor planning problems, gastrointestinal issues including gastroparesis, disordered sleep and sleep-related disorders, and dental issues.

Critical Management Issues

It cannot be overstated how important it is to properly manage the food environment for individuals diagnosed with PWS; not only does their physical health and safety depend upon it, their emotional wellbeing and behavioral interactions are equally dependent. With that in mind, the management of the hyperphagia and food-related behaviors is, in many ways, the easiest of the behavioral difficulties to manage. We turn to that issue first.

Managing the Food-Related Behavioral Constellation

Pharmacology and Medication While there is broad consensus regarding the need for pharmacologic treatments for ameliorating the hyperphagia and progressive weight gain in PWS, current standard therapies have not proven consistently effective. However, at the time of this writing, there are multiple clinical trials of various pharmacologic agents that ultimately may prove helpful in modulating the impact of the hyperphagia [29]. Thus, until a safe and effective medication is available, the life-threatening drive for food in individuals with PWS requires strict external/environmental control of food access and intake.

Behavioral and Environmental Management Experience of the past several decades has been instrumental in developing effective strategies for managing both weight and the accompanying food-related behavior constellation. Much of this understanding initially came from two populations of young adults entering group living settings: (1) young adults whose weight had been well managed and who were not and perhaps had never been obese; and (2) young adults who, prior to out-of-home placement, had been extremely obese but for whom placement allowed sufficient supervision and food management strategies to achieve necessary weight reduction. In addition, we now have the experience of caring for a generation of young adults, many of whom have reached young adulthood without ever developing obesity due to life-long strict dietary management supplemented with growth hormone replacement therapy. The lessons learned from these individuals have contributed to our current understanding of effective behavioral and environmental management of the hyperphagia and the accompanying food-related behaviors.

Effective management requires the unyielding presence of four environmental elements: (1) a physical environment structured so that food access is completely eliminated, (2) an appropriate dietary and exercise plan, (3) a procedure for

ensuring that the affected person is always informed regarding the time and menu for the next meal or snack, and (4) elimination of all other avenues for obtaining food. While at first appearing draconian, these proven measures rest on the principle of eliminating anxiety around food for the affected individual, which then eliminates the potential for behavior problems around food. Any access to food creates hope, and hope creates anxiety coupled with a focus on "how to get the food." Reducing or eliminating the anxiety eliminates unwanted food-related behaviors. Codified under the concept of "*PWS Food Security*" [78], the operating directive is *"No Doubt + No Hope = No Disappointment"* reflecting "no doubt when the next meal or snack will be served plus no hope or chance to obtain extra food means no disappointment; no disappointment means no food-related behavior problems." Within this over-riding environmental structure, a number of corollary principles emerge (see Table 12.3).

Where such stringent management is new to an affected individual, the person with PWS may initially act out and attempt to dismantle all newly established boundaries. For many, such behaviors have previously proven effective in undermining management attempts. However, with consistency and patience, this period of acting out usually subsides. Even when behavioral compliance has been largely achieved, frequent conversations about food may continue. Many routinely ask what will be served at the next meal, ask when the next meal will be served, ask how the food will be prepared, ask "Is it time yet?" and complain that there is not enough food, and request additional portions. Nonetheless, with management that is both consistent and stringent, behavior eventually stabilizes, and cooperation and compliance are less difficult to obtain. Parents and caregivers report that, over time, when the person with PWS realizes that excess food is no longer available, and knows the limits are effective and inviolable, there is an

Table 12.3 Food security principles

For the person with PWS
Scheduled Food should be like breathing. *NEVER* use food as a reward. *NEVER* use food as a bribe or incentive. *NEVER* withhold food for poor behavior.
Higher cognitive abilities and verbal skills do not equate to ability to override the brain's insatiable drive to obtain food.
People with limited intellectual functioning can be brilliant at obtaining food.
The ability to plan and execute complicated arrangements to obtain food may not generalize to abilities in other areas of life.
Even the most honest person with PWS may fib or steal when it comes to food.
Behavior problems are often related to potentially obtainable unsecured food sources. Once food sources are locked, anxiety is reduced and behavior problems in all areas are often reduced.
Do not remove food—or *any* item—from the hands of someone (unless dangerous or poisonous) as this will almost always create a behavioral outburst.
For the environment
Do not serve food "family-style" from the dining table. Instead, plate everyone's food at the stove and take to the table.
It is often all about quantity: use a smaller plate; cut food into small pieces; spread food out to fill entire plate; break chips apart so they look like more, etc.
If unauthorized food is known or suspected:
1. Do not question the consumption: "Did you eat those chips?" Rather, presume food was eaten and state as a fact: "I see the chips are gone."
2. Take responsibility for the individual gaining access to the food: "I'll make sure that doesn't happen again, so you stay safe."
3. Secure the food source.
4. Without the individual knowing, reduce calories in future meals to compensate for additional consumed calories.

observable and marked reduction in anxiety; many also can articulate feeling safer.

While simple in concept, realistically total elimination of food access can be extraordinarily difficult to accomplish, because to do so requires eliminating food and money accessibility *in every environment* including access to vending machines, the Internet, or even the remotest possibility of surreptitiously "running down the street to get a Coke." Food of one type or another is regularly found in virtually all human environments—classrooms, school buses, cars, offices, gymnasium dressing rooms, parking lots, playgrounds, and anywhere a trash can is present. Furthermore, many groups routinely fundraise with some food product: band candy bars, Girl Scout cookies, and fruit cakes and pecans during the holidays are some that may be more difficult to avoid. To fully "food-proof" an environment, it may be necessary to lock cabinets, refrigerators, doors to the kitchen, and garbage cans and to alter traffic patterns for delivering groceries. And, while a family or caregiving setting may be able to make these alterations, equally important, but often more difficult to manage, are additional environments where the affected person may spend time, such as schools, workplaces, recreational programs, churches, and shopping malls. Individualized Education Plans (IEPs) and Individual Habilitation Plans (IHPs) should specify the needed environmental safeguards as part of the plan. However, it is rarely enough to merely specify that environments should be food-free, even when those managing the various settings are fully cooperative. Even the best-intentioned schools, churches, or workplaces will find it challenging and sometimes impossible to eliminate food. For this reason, affected individuals often require the assistance of an aide or increased supervision of some form to prevent food access. While vigilance and awareness are always necessary, there will inevitably be slips that should be handled matter-of-factly and subsequent dietary intake adjusted. Even in well-monitored environments, it is essential to educate caregivers to detect and to deter the inevitable and often clever pursuit of food.

Extreme Cautiousness Using Food as a Reinforcer: Use Only as a Last Resort In addition to social praise and attention, a variety of non-food items and privileges can effectively serve as reinforcers for most individuals. Nonetheless, when several behavior change plans have proven ineffective, the possibility of using food as a reinforcer inevitably is raised. There currently are several points of view regarding this issue.

One point of view assumes that the nutritional management of PWS is analogous to, and as critical an issue as the dietary management of diabetes. Therefore, appropriate management includes a restricted diet developed in consultation with a nutritionist or clinical dietitian and the primary care physician. The degree of restriction depends on individual need; those needing to lose weight may require a more restricted caloric intake, while those needing to maintain weight or who are still in a growth phase may need a less restricted diet. A number of other variables impact caloric requirements, such as energy expended through exercise, use of supplemental growth hormone therapy, and the presence of diabetes. This point of view considers the use of food (primarily extra food) as a reinforcer "out of bounds" and a "never event." In this view, using (extra) food as a reinforcer sends a double message, is confusing to the individual, and undermines the critical *medical* aspect of dietary requirements. Thus, it follows as an absolute that any food that is *outside* the dietary and medical treatment plan cannot be used as a reinforcer. For example, a school setting that allows an "extra" Coke, candy bar, or ice cream to obtain compliance or alter behaviors would be considered both unsafe and medically inappropriate.

However, even within this framework, there are ways to effectively use food as a reinforcer, when safely incorporated within the dietary and medical treatment guidelines. For example, individuals with Prader-Willi syndrome rarely eat indiscriminately and have individual food preferences that remain constant [79, 80]. Appropriately structured, these preferences can be employed as

reinforcers. Thus, providing a preferred (and allowable) breakfast food choice (e.g., Cocoa Puffs) can be made contingent on timely completion of a prespecified behavior (e.g., being up, dressed, and ready for school or appointment on time). Similarly, special restaurant visits or trips to a store to purchase an allowable food item may be used as a one-time reinforcer or on a regular schedule based on meeting certain specific behavioral goals over time (e.g., being up on time and ready for school on time for a week). In some instances, very low-calorie food items such as sugar-free candies, drinks, or gum may serve as strong reinforcers without significant impact on overall caloric consumption.

In the case of critically important behavior, a specific portion of daily calories may be allocated for use as reinforcement or extra calories may be allowed based on meeting specific calorie burning exercise requirements. For example, Keefer [81] examined the exercise behavior of seven individuals with Prader-Willi syndrome. None of the participants in this study exercised during baseline observations. Initially, most of the subjects engaged in some exercise with just verbal prompting. However, even with verbal encouragement, exercise participation diminished over a period of a few days for all but one individual. In phase two, the remaining six individuals were then provided with either "extra" calories (usually 100 calories) to be used at their discretion or specific extra food items based on completing exercise requirements. All of these participants resumed exercise and ultimately met the program goal of exercising continuously for 45 min, three times a week, and their hearts remained in a beneficial aerobic zone. One individual who weighed 500 pounds at the start of the study lost 180 pounds during the course of the project. Notably, no negative behaviors were observed associated with program participation. Predictably, there were problem behavior incidents from participants who exercised but whose efforts failed criteria for earning extra calories. There were no reports of obsessive verbalizing about the exercise or calories being earned.

A different point of view holds that, when used appropriately and integrated into the overall dietary plan, food is an especially powerful reinforcer in this population. Thus, supporters of this strategy assert that it would be a disservice to fail to take advantage of edibles as a reinforcer when either addressing problem behaviors previously resistant to change or when establishing critical behaviors such as exercise or cooperation with medical procedures or therapies. Since food is an especially powerful reinforcer, its use for reinforcement should be reserved for priority behaviors.

However, even those who embrace this point of view assert that *any* use of food as a reinforcer should be approached with caution, since the effects of any reinforcement procedure depend on establishing an appropriate link between the desired behavior and the reinforcer and reliably implementing the procedure. To avoid reinforcing inappropriate behavior, food should never be provided during a behavior incident as a means of stopping the behavior or gaining compliance. Similarly, food should never be provided in response to a threat (e.g., "Give me food or else."). Correct use of food as a reinforcer requires documentation that the individual can perform the desired behaviors. If appropriately designed, the reinforcer will be earned more often than not. The reinforcement plan should be discussed in advance with the participant at a time and place away from any behavior problem incident and in a private location free from interruption. When individuals participate in the development of their own behavior plan, there is greater compliance and an increased likelihood of success. To ensure that the plan is clear to the participant, it is helpful for the individual to restate the plan, specifying the expected behavior and the consequences for meeting and not meeting expectations. A written behavior contract can be an effective method for setting up such plans.

Strategies for Effective Behavior Management

Providing the Foundation for Positive Behaviors: General Strategies and Approaches to Intervention Successful behavior management requires at least three elements: (1) a con-

sistent, supportive environment; (2) strategies for promoting positive behavior; and (3) strategies for managing difficult behavior. Following a review of these elements, we provide some specific behavioral suggestions for preventing and managing behavior at home, school, or work. These are provided in a table that can be copied and used for planning and managing behavior on a daily basis. Applied Behavior Analysis (ABA) is frequently raised as a general behavior management intervention strategy for developing positive behavior and reducing unwanted behavior. Indeed, its use in multiple populations has been well researched and validated, especially in those with autistic spectrum disorders. However, its use and application to those with PWS has been less than successful and should never be used to address food-related behaviors [82]. If ABA intervention is considered, its use should only be attempted by someone well-schooled in the special behavioral characteristics of those with PWS and certified in ABA as well.

Environment Affects Behavior It has long been accepted that much of our behavior is influenced and controlled by the environment. The environment includes not only the physical setting, but more importantly the interactions between the individual with PWS and everyone else in that environment. In addition, it is well accepted that many individuals with PWS have a heightened sensitivity and reactivity to their environment. Persons with PWS tend to over-emphasize and over-react to the negative aspects (real or imagined) and under-recognize and react to the positive aspects of the environment. Thus, the role of the surrounding environment in supporting or impeding positive behavior management and positive adjustment for those with PWS cannot be overemphasized.

Depending on the degree of structure, environments (work, school, home) can be categorized along a continuum from chaotic, to flexible, to structured, and finally to rigid [83]. Chaotic environments have insufficient structure and rules; at the opposite end of the continuum, rigid environments are fixed, inflexible and do not allow for positive changes. Both of these polar opposite environments tend to undermine the healthy functioning and adjustment of those in such environments. Flexible and structured environments provide a set of operating rules and routines that are supportive but are open to review and change when needed for improved functioning of those in the environment. Individuals with PWS who have a reduced ability to be flexible, and have difficulty with uncertainty and unpredictability, function best in (highly) structured and predictable environments. For the person with PWS, knowing the rules, routines, and expectations reduces anxiety, thereby reducing the potential for reactivity and escalation that can lead to unwanted behavior.

Environmental Basics In general, the environmental structure for those with PWS should include (1) those inviolate routines and "family and house rules" regarding what is expected, acceptable, and unacceptable behavior, along with specified consequences for misbehavior that are consistently administered; (2) schedules that are, as much as possible, invariant in time and task routines; (3) clear boundaries that define and provide structure to relationships; (4) calm responses from caregivers; and (5) consistency between parents or caregivers. It cannot be said enough, consistency across environments and caregivers is critical since inconsistency increases anxiety and invites frustration that can escalate to unwanted behavior.

Rules Rules define acceptable and unacceptable behavior, along with specified consequences for misbehavior. Persons with PWS are rule followers. Knowing the rules makes it easier to obtain success. Knowing the rules also reduces anxiety. When something is understood as a rule, it is more likely be adhered to, *especially* if the individual had input to create the rule. A few tips for developing the rules are as follows:

- Establish the rules for chores (make bed in the morning, set table for supper), hygiene (wash hands after restroom), exercise/activity (walk first then snack), social rules (greetings, shar-

ing), shopping (no whining), food rules: restaurant rules, buffet rules, party rules; telephone, Internet, and game/tablet use… essentially rules for *everything*! While establishing what is expected, the use of rules and routines can also serve as the basis for behavior performance charts when needed.
- Post the rules so they are visible or easily seen until they are learned. This serves two purposes: (1) it is a constant reminder of the rules and (2) when an argument is about to start, pointing to the written rules makes the issue a function of the rule and not a disagreement between two people. Always be sure to have an extra copy for those occasions when the person with PWS angrily says "I don't like the rules" and tears them up.
- Be sure to establish the rule that parents or care providers can change a rule if necessary!

The goal is to establish parental or care provider authority ("We need to do it"), not to be authoritarian ("Do it because I said so"). Authoritarian responses often *cause* behavior problems.

Routines (and Schedules) Persons with PWS have a high need for routine, predictability, consistency, and sameness in the environment. Create routines for every aspect of the day: bedtime, wake-up time, getting ready for school or work in the morning, meals and snacks, medications, chores, telephone, Internet, and game/tablet use. Some suggestions are as follows:

- Create written or visual schedules or charts for daily activities, chores. Words combined with pictures are best.
- Refer to the written schedule to avoid disagreements.
- Provide advance notice, as appropriate to the individual, about necessary changes in plans and routines, and mark this on the visual schedule as soon as known. When approaching the anticipated change, verbal reminders such as "remember we are changing things a bit tomorrow" are often helpful.

Boundaries Boundaries define limits and provide structure to relationships. Boundaries establish what behavior is and is not acceptable. Firm boundaries also reduce anxiety and help people feel safe. Boundaries are *critically* important to persons with PWS. Clear and firm boundaries keep the world predictable and safe and function like a lifeline from the free-floating anxiety that is prevalent in so many with PWS.

- Define and uphold your boundaries with authority:
  - Teach appropriate communications: teach the individual to be well-mannered, polite, assertive, and direct in their communication; no whining, demanding, passive, aggressive, or passive-aggressive behavior.
  - Teach appropriate physical proximity: establish physical boundaries with strangers, acquaintances, friends, family, etc.
  - Teach appropriate accessing others' property: distinguish permission vs. theft.

Do not give the individual with PWS too much power. If you concede too frequently, the hierarchy of power is turned upside down, safety is breached, anxiety is increased, and unwanted behaviors will increase and escalate in intensity. Parents and care providers *must* be perceived as the authority and inhabit the Parental Authority Position so that the individual with PWS can feel safe and protected. Some boundary tips are as follows:

- Stop unintentionally and inappropriately asking permission. For example, avoid "You need to stop jumping on the bed now, *okay*?" Or "You need to stop taking your brothers chips, *okay*?"
- Say what specific behavior you *want*, not only what you *do not* want. For example, "Stop jumping on the bed. Put your feet on the floor please." "I don't understand whining. Please use a clear voice." "I've answered that question three times so as I told you, I won't talk about that anymore."

- Do not repeat requests more than 3 times. At your third request, physically and calmly begin to intervene. For example, walk over to individual while stating, "It looks like you need help to keep your feet on the floor."
- State and stick to your boundaries regarding time limits, rules, routines, permissible language, and behavior. For example, *I want sugar in my coffee.* "I know you like sugar. We don't use sugar though. If you don't want black coffee you don't have to have coffee today."
- Use transition cues including verbal countdown prompts. For example, "Five minutes until the show is over and it will be time for bed." Use auditory alarms, visual countdown timers, etc.
- Do not lie in attempt to avoid a situation *especially* if it is possible your deceit will be discovered. For example, if you are eating something do not say, "No, I am not eating anything." You *must* be perceived as honest.
- Avoid ambiguity. "We'll see" or "Maybe later" are vague and may create anxiety. If you do not know, say, "I don't know, I'll let you know as soon as I do."
- Avoid open-ended questions which can be difficult to process and create anxiety. Give two to three preferred choices.
- Say what you mean and mean what you say. Do not promise anything you do not intend to follow through on. You *must* be the reliable authority.
- Do not threaten to remove a privilege that you do not intend to complete. Removing privileges or taking something away can be tricky as it often leads to *more* behavior problems, and generally does not teach cooperation. If appropriate, provide opportunity to earn a revoked privilege right back.
- Do not allow yourself to be manipulated. Remain in the authority position.

Rules, Routines, Boundaries, and Choices—Creating the Win-Win While providing the appropriately structured environment, the rules, routines, and boundaries must also provide *carefully designed* opportunities for the individual to make choices. One aspect of that design is the avoidance of open-ended questions. For individuals with PWS, open-ended questions tend to create anxiety which then creates the potential for unwanted behavior. Additionally, open-ended questions also create the opportunity for disappointment which, again creates the potential for unwanted behavior. A simple example will illustrate. If Mom asks in an open-ended fashion, "What do you want for breakfast?", it suggests (1) that all choices are valid and available, and (2) that any requested choice will be provided. When the answer is "chocolate cake," the obvious response from most mothers will be, "You can't have chocolate cake for breakfast!" To the person with PWS, the offer implying an open-ended choice followed by a denial of the selected choice is confusing and *feels punitive,* raising the probability of a reactive tantrum. *However,* if Mom asks, "Do you want eggs or oatmeal for breakfast?" she is still offering a choice, but one that is possible and positively structured within the dietary plan, and at the same time provides the person with PWS a choice and a sense of personal control. For both Mother and the person with PWS, the choice has been structured as a win-win outcome. If the person with PWS answers, "I want (something different)," Mother has two options. She can respond, "That was not one of the choices; you need to pick either eggs or oatmeal," or she can respond, "OK, just for today I'll allow another choice." Whether Mother allows a different choice, this one time in part depends on Mother's previous experience with this child and her assessment of whether granting this one exception is likely to lead to future perseverative or escalating pleading for more exceptions. When as many positively structured choices as possible are a routine part of daily living, many areas of power struggle and frustration are avoided.

Calm Responses from Persons in the Environment When speaking with someone with PWS, it is critically important to keep negative emotion out of your voice since (1) the

individual is very likely to over-react to your emotional tone; (2) anxiety is significantly increased by raised, critical, accusatory, or angry-sounding voices; and (3) the individual will cease processing and responding to your words as they react to your emotional tone. No matter how upset the individual with PWS becomes, a calm response from *you* reduces their anxiety. Termed "low-expressed emotion," it is a critical skill for preventing escalation of noncompliant and disruptive behavior, and for de-escalating already out of control behavior. Some tips include the following:

- Always speak calmly despite how you feel on the inside, *especially* during emotionally charged exchanges.
- Persons with PWS typically like "drama." Some are "pot stirrers." Do not engage.
- Listen to the individual who says, "Leave me alone." Do not say anything else, do not look directly at them, do not stand close. Monitor with peripheral vision and let them cool down.
- Respond to a tantrum, an escalation, or a sit-down strike with indifference or boredom. Ignore unwanted behaviors to extinguish them as quickly as possible. Read a book or engage in other similar activities to project "boredom."
- Match the demands on the individual to their ability.
- Breathe. Care providers often find it difficult to remain calm when under stress, yet we expect our loved one with a serious developmental disability to remain calm under stress. We need to take care of ourselves "well enough" in order to care for our loved one "well enough." When dealing with episodes of misbehavior, remember to breathe, focus on the breath, relax. Breathe, relax. Breathe, relax.

Consistency Between Parents or Caregivers It cannot be over-emphasized that consistency across environments and caregivers is critical since inconsistency increases anxiety, invites frustration that can escalate to acting out, and in many instances teaches the person with PWS how to be manipulative. To illustrate, suppose the family has gone out to eat and has not fully prepared the person with PWS regarding what they will be allowed to order. Mother says "you may have X," to which the person with PWS reacts, says "I don't want that," and starts to get loud. At that point Dad says, "I don't want to deal with a scene, let him have what he wants this time." For the person with PWS, that is like a free pass to act out in the future, because the lesson that has been learned is if I want something and Mom says no, all I have to do is act out, especially in public, and I will get what I want. That same analogy applies to differences between staff on two different shifts. Staff on shift X may stick to the "rules," while staff on shift Y gives in to misbehavior. Over time, it becomes obvious that most misbehavior occurs on shift Y, and often when confronted, the individual "fesses up" that when they misbehave on shift Y, they get what they want.

General Tools and Strategies for Promoting Positive Behaviors and Managing Challenging Behavior

While the best approach for managing difficult behavior is prevention, it is a given that behavior problems will occur. How these are handled is critical to a successful resolution of the behavior and to preventing recurrence. The success of behavioral interventions hinges on the ability of caregivers to provide the necessary intervention with consistency and integrity. Unlike traditional behavior change programs and methods, the goal for the person with PWS is to continuously manage the individual's environment and circumstances in order to prevent unwanted behaviors rather than expecting long-term, permanent behavior changes. In some cases, a professionally designed behavior change program may be necessary to produce an acceptable behavior improvement. This section begins by describing

general behavior analytic principles and change strategies, and then focuses on the application of these principles to those with PWS. The use of medication as a tool for behavior management is addressed in Chap. 22 and will not be dealt with in this chapter.

Behavioral approaches are based on appropriately managing the consequences of behavior. The most effective behavioral approaches include a general strategy of giving positive consequences for positive behaviors and *avoiding* the use of negative consequences such as punishment or coercion to achieve behavior compliance. This is especially true for those with PWS, as punishment is singularly unsuccessful in achieving behavior improvement. In fact, punishment usually elicits stubborn reactivity, an escalation of unwanted behaviors, and frequently pushes the individual to a "meltdown." While some caregivers may then have a natural instinct to apply an even more severe punishment, this strategy has never been found to be effective in this population. To learn through punishment "a person needs skills typically lacking in persons [with PWS]: insight and ability to problem-solve; memory, logic and ability to rationally build on past experiences; ability to compare and discriminate information; ability to recognize the value of an experience and learn from it; and the ability to think sequentially (first this, then that; if this, then that)."

Similarly, the use of coercion which includes questioning, arguing, threats, verbal or physical force, criticism, and revoking privileges also is usually counterproductive. In addition, coercive responses are usually accompanied by a negative emotional tone indicating frustration and even anger on the part of the parent or caregiver. While coercion may stop a specific instance of a problem behavior in the short run, over time coercion makes things worse as such techniques motivate the desire to escape and to avoid the people and circumstances associated with the coercion. Coercion can also directly trigger inappropriate emotional behavior and often motivates the individual to retaliate or get even with people and places associated with the coercion. These common effects of coercion may be heightened in individuals with Prader-Willi syndrome, who are known for their emotional reactivity and lability.

While recognizing the power of positive consequences for strengthening appropriate behavior, research also documents that many problem behaviors *inadvertently* are maintained by *inappropriate* social attention to the behavior. Coercive techniques provide inappropriate social attention to problem behaviors. Paradoxically, to the person with PWS, coercive techniques inadvertently can provide wanted social attention that then serves as an unintended, *positive* consequence to their inappropriate behavior, thereby directly strengthening further occurrences of these behaviors.

As with the dictum to maintain a food safe environment, the dictum to avoid coercion may be easier said than done. When a youngster is not performing expected behavior or is displaying inappropriate behavior and fails to respond to requests for appropriate behavior, it is only natural to reactively comment on the "misbehavior" by scolding or threatening with negative consequences and to do so using a voice tone that indicates frustration or anger on the part of the parent or caregiver. As previously indicated, individuals with PWS are very likely to over-react to these coercive techniques and the accompanying negative emotional tone. Thus, it is important to recognize when a coercive interaction is taking place and shift to a more positive approach.

Among those with PWS of any age, separate from the food-related concerns, tantrums are perhaps the most frequently reported example of noncompliant and disruptive behavior [84]. For many, such behavior is the limiting factor in maintaining an integrated school setting, a group home placement, or a job. Almost all children exhibit tantrum behavior between the ages of 2 and 3 years of age, and tantrums are a normal part of childhood development as the young child learns he is a separate being from mother or father. Due to developmental delay, most children with PWS sail through what is typically termed the "Terrible Twos" and do not begin to

exhibit "typical tantrum behavior" until age 3 years. While most typically developing children eventually learn healthier and more socially appropriate ways to obtain what they need, individuals with PWS continue to display behavioral and emotional reactivity through tantrum-like behavior across the life span. Tantrums may be triggered by many situations such as a poorly negotiated required transitions, an unexpected change in routine, not getting one's way, or having one's expectations disappointed. In general, tantrum behaviors may cease when (1) the individual receives what he or she wants; (2) when the individual is satisfied with some sort of compromise; or (3) when the individual ultimately accepts they will not get what they want and gives up. However, there are instances when an individual may become so frustrated that their tantrum behavior is unsuccessful in securing what they want that they may become completely immersed in their frustration and anger. Termed a "meltdown," this represents one of the more challenging of PWS's maladaptive behaviors, and depending on how managed, can lead to acting out through physical aggression, verbal aggression, destructive behavior, or attempting to elope.

Many parents make the mistake of giving in to a tantrum because they believe the child will "grow out of" this behavior eventually, or because they simply want to avoid the escalation of tantrum behavior, especially if in a public setting. It cannot be stated more strongly, caregivers *must not* give in to a tantrum. Remembering the rules of behavior management and the management of consequences, then it follows that giving in to a tantrum is providing positive consequences for bad behavior. By giving in to a tantrum, the unintended lesson that has been taught is to get what is wanted, one simply has to yell louder, for a longer time, perhaps even become verbally and physically aggressive, and eventually the tantrum will be rewarded when the caregiver concedes. It is critical to directly and specifically teach the child with PWS that their tantrum behavior will *not* get them what they want, and to specifically teach them healthier and more socially appropriate ways to obtain what they need. Tantrum behavior that is not appropriately addressed with PWS-specific behavior management strategies will likely continue to escalate and worsen, leading to more frequent and destructive meltdown behaviors.

If a caregiver has given in to a tantrum, the following strategies can be helpful in remediating the situation:

1. Explain that past giving in has not been helpful.
2. Apologize for past goof (if appropriate).
3. Explain that from now on, *for the individual's benefit*, you will not give in and will work hard to keep them safe.
4. When a tantrum for something subsequently begins, the caregiver should calmly remind the individual that their behavior will not get them what they want, and that the caregiver will not give in because that is not fair to them.

Avoiding Tantrums and Meltdowns: Empathy as an Intervention A powerful first-line intervention to respond to an upset or disappointment and avoid tantrum or meltdown behavior is to use empathy as an intervention. Cognitive empathy is the ability to understand and perceive things from another's perspective. Most individuals with PWS are egocentric, lacking the ability to see things from the other's perspective and thus only able to understand things from their own myopic viewpoint [73]. It is helpful when individuals with PWS have people in their environment who possess some degree of empathy and can reflect an understanding about what it is the individual with PWS is upset or concerned. Empathy is neither agreeing nor disagreeing, and it is absolutely not giving in: It is simply communicating that you understand the perspective, want, need, or concern of the other. In its simplest form, empathy can be conveyed simply by listening to and repeating the individual's own words. Understanding the concern *from their perspective* helps the individual with PWS feel understood.

Once feeling understood, most individuals with PWS typically do not need to get louder or more aggressive ("turn up the volume") in attempt to get you to understand them.

Words or phrases that instantly convey empathy that can be used include the following:

- "What a bummer!"
- "What a disappointment."
- "That's not fair!"
- "It sounds like you would like to xyz. Is that right?"
- "You want xyz. You want xyz. You want xyz."
- "I get it. You would like to xyz."
- "Xyz won't work. I hear you. Xyz won't work."
- "You think x. I understand that you think x."

Until empathy as an intervention is employed, attempts to use logic or reasoning to talk the individual out of their upset will typically *increase* the upset. Escalating maladaptive behavior is often terminated as soon as the individual believes their upset or concern is genuinely understood and will be addressed.

Only after individuals with PWS believe that a caregiver completely understands *their* concern and anxiety starts to dissipate, should the caregiver share *their* concern or move toward solution. One should not attempt to problem-solve *for* the individual; due to the inherent oppositional nature of the behavior phenotype of PWS, it is highly likely that any solution suggested, despite its brilliance, will be summarily dismissed. Instead, one should "lead" the individual toward developing his or her own potential resolution or compromise. If the upset returns, simply revert to employing empathy as an intervention.

Inexperienced care providers are often fearful that using empathy as an intervention—repeating and reflecting the individual's expressed upset—will create *more* upset. This rarely occurs. In fact, the *more* the expressed upset is reflected, the *faster* the individual with PWS feels understood and calmer. If upset escalates after genuine empathy is repeatedly expressed, respond thereafter with steadfast indifference.

Prevent Upset in New Settings: Paint the Picture, Rehearse Appropriate Behavior Responses For the individual with PWS, knowing what to expect reduces anxiety and thereby reduces the potential for unwanted behavior. Before entering *any* situation, one should explain in detail what will happen, what things will look like, what are the expectations for behavior, and what the plan is if unwanted behavior occurs. One should "Paint the Picture," *especially* for doctor appointments, waiting rooms, restaurants, stores, events and parties, and family gatherings. Many caregivers and individual with PWS find it helpful to "rehearse" ahead of time and practice some possible responses for different situations and behaviors that might be encountered. By so doing, when in the situation where anxiety and a possible negative behavior starts to build, a soft reminder "remember we rehearsed that" can be very effective in lowering anxiety and preventing further escalation. Additionally, always remember to bring toys, books, puzzles, etc., to keep the individual busy during wait times. Reward *constantly* with praise and small tokens for waiting well and for a successful event.

Prevent Frustration: Disguise the "No" The word "no" is a frustrator signal to an individual with PWS. The word "but" is also a frustrator. Caregivers should use them sparingly and "disguise" them whenever possible. As an example, the individual with PWS says, "I want to go outside." The parent/provider reply might be, "Me too! It looks fun out there! As soon as we finish our work we will go outside!" as opposed to "No, we cannot go outside until our work is finished."

Meltdown Insights Despite the best preparation and caregiver responses, occasional meltdowns are inevitable. In that situation, it is important for caregivers to recall the following tips:

- Once a genuine meltdown has begun, caregivers must wait it out and work to keep the individual and others safe.
- After a meltdown, people with PWS often feel sorry, embarrassed, or shameful. Comfort should be provided to the individual without condoning the unwanted behavior.
- Caregivers should accept an apology if offered, but they should not let the absence of an apology become another power struggle. Similarly, an apology should not dismiss the need for consequences when appropriate (e.g., cleaning up a room that was torn up during the meltdown; helping pay for broken items that belong to others).
- The intensity of the person's remorse does not reduce the likelihood of the same thing happening again.
- Later, when everyone is calm, it may be possible to go back and examine what happened.

Other Helpful Behavior Strategies

In addition to praise and attention, individual preferences usually offer a variety of other items or privileges that can successfully reinforce appropriate behavior [85]. A powerful tool for making use of such reinforcers is the "behavior contract." A behavior contract is a written agreement that an individual will earn a desired item or privilege, based on the occurrence of a specifically defined behavior. Behavior contracts are usually used to address persistent problem behaviors, establish new responsibilities, or improve performance when the individual's responses have been inconsistent. For example, if an individual with Prader-Willi syndrome has trouble getting up and getting ready for school or work in the morning and prompting this behavior often leads to tantrums, a contract may be helpful in addressing the morning routine. A contract must specify all tasks to be completed, completion times (e.g., fully dressed and in the kitchen by 7:15 a.m.), and other attitudinal or behavioral parameters (e.g., speaking with an inside voice rather than yelling, as in a tantrum). The contract should also specify a daily consequence for completing these tasks (e.g., sticker on a wall chart) and a long-term consequence (e.g., trip to the pet store) for consistent completion of these tasks (e.g., 4 out of 5 weekdays). Once the behavior is occurring consistently, the tangible reinforcer can be used to address another behavior, and the original behavior can be maintained by the occasional praise and more natural consequences.

Finally, dangerous behavior or behavior that is too disruptive to ignore can be addressed with the "stop-redirect-reinforce" technique. This tool requires (1) immediate termination of the behavior by interrupting it verbally and physically, (2) verbal redirection to an appropriate behavior (related, if possible), and (3) immediate provision of positive attention when the redirected (or any appropriate) behavior occurs.

In addition to these general principles, Table 12.4 provides some specific tips and techniques found to be effective.

Table 12.4 Behavior management strategies for home and school

Common behavior characteristics in youngsters and adults with PWS	Possible management strategies	
	Home	School or workplace
Rigid thought process and inability to be behaviorally flexible Youngsters and adults with Prader-Willi syndrome have a hard time being flexible and accommodating changes of schedule and routine. Most have an instant reaction to changes in routine or expectations, trouble with routine transitions such as moving from one school subject to another, and problems with uncertainty and ambiguity. It is also common for people with PWS to receive and store information in a single order, so that they must go through the whole order to get any one piece. Thus, there is a strong need for routine, sameness, and consistency in the learning environment. Because of a problem in sequential processing, students or employees are not always able to turn *what not to do* into *what to do*.	Provide weekly and daily schedules in visual form. Provide verbal anticipation of changes and allow for discussion, such as "five minutes till we leave." Do this in a safe area where person with PWS can share feelings. (The youngster needs time to adapt to this change.) Plan ahead to allow extra time. If there is a change, use visuals; put things in writing, such as in lists and schedules (correct when changes are made). Do not make promises you cannot keep. Break down tasks and activities into concise, orderly steps. It is often helpful to provide pictures of the youngster/adult performing the tasks and activities. Use empathy. Offer preferred choices. To resolve "stubborn issues," try using compromise. Both the caregiver and the youngster/adult must come up with a totally new solution. Not only is this a successful problem-solving strategy, but it can also be a form of diversion. Provide praise when being flexible.	Provide weekly and daily schedules in form and, where needed, pictures of the youngster/ adult performing tasks and activities. Provide verbal anticipation of changes and allow for discussion. Do this in a safe area where they can share feelings. (The student needs time to adapt to this change.) For routine transitions, provide verbal anticipation. For example, "five more minutes and we finish this project" or "in five minutes we start today's math lesson." Individual timers at the desk can also be helpful. If there is a change, use visuals; put things in writing, such as in lists and schedules (correct when changes are made). Do not make promises you cannot keep. If able, communicate changes in personnel ahead of time (but not too far ahead). Break down tasks and activities into concise, orderly steps. For many youngsters, it is helpful to provide pictures of the youngster/ adult performing tasks and activities. Use empathy. Offer preferred choices. To resolve "stubborn issues" try using compromise. Both the student and the educator have to come up with a totally new solution. Not only is this a successful problem-solving strategy, it can also be a form of diversion. Provide praise when being flexible.
Concrete thinking Persons with PWS are generally literal, concrete, surface thinkers and have great difficulty with abstract (in-depth, reflective) thinking. Many also lack what is generally termed "common sense" thinking. In this population, higher cognitive or IQ scores do not necessarily mean better judgment, more "common sense," or better problem-solving skills.	Abstract concepts such as time and time management can be especially difficult. Use visuals including visual schedules, egg times, or other timers. Specifically teach metaphors such as "the snow is like a white blanket." Specifically teach idioms and point them out when others use them, for example, "she has cold feet" means she is nervous.	Abstract concepts such as time and time management can be especially difficult. Use visuals including visual schedules, egg times, or other timers. Specifically teach metaphors such as "the snow is like a white blanket." Specifically teach idioms and point them out when others use them, for example, "she has cold feet" means she is nervous.

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Table 12.4 (continued)

Common behavior characteristics in youngsters and adults with PWS	Possible management strategies	
	Home	School or workplace
Egocentric thinking Persons with PWS generally think about themselves first and foremost. It is very difficult for them to see things from someone else's point of view. Pointing out that the person with PWS needs to consider the other's point of view or need often results in more rigid fixation on what the person with PWS wants or thinks, so careful phrasing of requests or demands is key.	Do not say "If we don't hurry, Grandma will be late for her appointment." Do say, "If we get Grandma to her appointment on time, you and I will have time to watch a movie." Use egocentric thinking to your advantage. For instance, "Now that you are 25 years old, I'm thinking you are mature enough to sort the laundry. I'm not sure though, do *you* think you're mature enough?" For some with higher functioning cognitive skills, teaching the other's perspective can be helpful. "What do you think they're thinking?" or "What do you think they meant?" Pausing during TV shows, movies, commercials, etc., to talk about the other's perspective can help teach this skill.	Do not say "Your yelling is disturbing the family/class/residents/workplace." Do say "I hear you want xyz. When you speak softly/calm your body, we can talk about how to get it." Use egocentric thinking to your advantage. For instance, "Now that you are 25 years old, I'm thinking you are mature enough to sort the laundry. I'm not sure though, do *you* think you're mature enough?"
Need to be right/good/competent One aspect of egocentric thinking is the perception that their opinion or information is always right. Any attempt to correct that thinking with different information can lead to disagreements that quickly become power struggles or provoke meltdowns.	DO NOT ARGUE, instead respond with neutral phrases such as "You might be right," "That's an interesting thought," or "Hmm, you think X and I think Y. I wonder why that is…"	DO NOT ARGUE, instead respond with neutral phrases such as "You might be right," "That's an interesting thought," or "Hmm, you think X and I think Y. I wonder why that is…"
Oppositional thinking Difficulties with processing language, slow cognitive processing, the need for sameness, and the wish to be independent taken together frequently result in the person with PWS automatically answering most queries with "no" even when they mean "yes." This can lead to reactive behavior problems when the affected person does not understand why people did not understand that they really meant "yes."	Avoid yes/no questions. Avoid open-ended questions that require a structured verbal response; provide the perception of control but minimal actual control. To accomplish this, present queries/expectations in a "win-win" format. For example, "Do you want to wear the red jacket or the blue jacket?" or "Do you want to hold the cart or my hand?" or "Do you want to shower in 5 minutes or 8 minutes?" NEVER ARGUE—usually given time, even when the answer has been an automatic no, the requested behavior will be forthcoming.	Avoid yes/no questions. Avoid open-ended questions that require a structured verbal response; provide the perception of control but minimal actual control. To accomplish this, present queries/expectations in a "win-win" format. For example, "Do you want to wear the red jacket or the blue jacket?" or "Do you want to hold the cart or my hand?" or "Do you want to finish reading in 5 minutes or 8 minutes?" NEVER ARGUE—usually given time, even when the answer has been an automatic no, the requested behavior will be forthcoming.
Low internal motivation Most persons with PWS have low internal motivation but may respond well to external motivators.	Use external motivators such as verbal praise, excitement and enthusiasm, music or musical games, good-natured competition (e.g., I bet you cannot beat me to the car), stickers, earned time with someone special, allow the individual to be your "helper,", or a visual token reward system.	Use external motivators such as verbal praise, excitement and enthusiasm, music or musical games, good-natured competition (e.g., I bet you cannot beat me to the room), stickers, earned time with someone special, allow the individual to be your "helper" or "line leader," or a visual token reward system.

Table 12.4 (continued)

Common behavior characteristics in youngsters and adults with PWS	Possible management strategies	
	Home	School or workplace
Self-monitoring deficits The ability to monitor oneself and accurately evaluate and moderate one's performance is often impaired.	Continuously remind to speak slowly; slow down eating, etc. Monitor for safety.	Continuously remind to speak slowly; slow down eating, etc. Monitor for safety.
Perseverative or obsessive thinking This is the tendency to get "caught" or "stuck" on one thought, question, or issue—to the point where it overshadows all other thoughts and activities. This behavior can contribute to difficulty in transitioning from one topic/activity to another. Since affected individuals often have a great need to complete tasks, if they are stuck it can lead to loss of emotional control.	If the obsessive thought or repetitive behaviors do not interfere with the flow of the day, ignore. If you have answered several times already, use reflection—have youngster/adult restate what you said. Put it in writing; use visuals. Carry a small notebook if needed. Depending upon the individual's abilities, less is best—give one direction at a time and allow completion before the next direction. Avoid power struggles and ultimatums. Ignore (if possible). Do not give more information than is necessary, especially too far in advance. Use "strategic timing"—schedule an activity that the youngster/adult has difficulty ending for right before snack or lunch. Set limits: "I'll tell you two more times, then we move on to next topic. This is #1."	If the obsessive thought or repetitive behaviors do not interfere with the flow of the day, ignore. If you have answered several times already, use reflection—have youngster/adult restate what you said. Put it in writing; use visuals. Carry a small notebook if needed. Depending upon the individual's abilities, less is best—give less amount of work at one time rather than more. Add to the work as time allows. Avoid power struggles and ultimatums. Ignore (if possible). Do not give more information than is necessary, especially too far in advance. Use "strategic timing"—schedule the activity that the student has difficulty ending for right before snack or lunch. Set limits: "I'll tell you two more times, then we move on to next topic. This is #1."
Collecting and hoarding A variant of perseverative and obsessive thinking is collecting and hoarding. If one is good, 100 is better. Sorting, pulling, tearing, and stealing may also be seen.	Limit collections to a certain space or number. When limit is reached respond with "you already have X, or you have filled that space. Before you can get another, you must get rid of (specify number)." Many affected individuals like to obsessively/ritualistically tear paper—provide a space for the behavior and provide old papers.	Limit collections to a certain space or number. When limit is reached respond with "you already have X, or you have filled that space. Before you can get another, you must get rid of (specify number)." Many affected individuals like to obsessively/ritualistically tear paper—provide a space for the behavior and provide old papers.

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Table 12.4 (continued)

Common behavior characteristics in youngsters and adults with PWS	Possible management strategies	
	Home	School or workplace
Tenuous emotional control or short frustration tolerance Any combination of life stressors can lead to emotional "dyscontrol." The result may be exhibited as impulsivity or as challenging behaviors such as tantrums—yelling, swearing, aggression, destruction, and/or self-injury. During these episodes, the ability to reason is overridden by emotion.	Be aware of "person/environment overstimulation"—for instance, large family gatherings, church settings, malls, and grocery stores. Have a previously practiced time-out procedure to allow calming down when getting overstimulated and give praise for using. Note that time out should never be used as a punishment, but as a positive step for allowing calming down and avoiding escalation. Start the day off on the right foot by allowing time to go over the schedule for the day and work through any changes there may be. Putting the new schedule in writing often helps to decrease anxiety. At the start of the day, set daily behavioral expectations *with* the youngster. Limit to no more than 3. Communicate behaviors *you wish to see*. Make it a cooperative task that provides concrete behavior expectations. Put goals in writing. Avoid the word "Don't," focus on the word "will" (e.g., "I *will* talk in a quiet voice" instead of "Don't yell."—"When I feel frustrated, I *will* tell Mr. Smith or another adult.") Provide positive attention and praise when youngster/adult is maintaining control, especially in difficult situations. Celebrate success! Encourage communication and acknowledging feelings. Words are important—Listen carefully! Include the individual in behavior plans. Having their input elicits cooperation and a sense of support. Be a role model: "I always say 'darn' when I am angry. Let's try that for you … darn, darn, darn." Practice when the youngster/adult is *not* agitated or angry. Depending on the youngster/adult and the situation, use humor. It is often effective. Similar to the process for overstimulation, anticipate build-up of frustrations and help him/her to remove self to "safe area." Create a key word or phrase that will alert the student that it is time to go. Practice using these words/phrases when the student is calm. Develop a plan and rehearse with the youngster/adult *what to do* if he/she feels angry or frustrated. Many individuals substitute a means of releasing this pent-up anger—long walks/exercise, ripping paper, tearing rags, popping packaging bubbles. *Do not try reasoning when individual is out of control. Limit discussion.* Provide positive closure. Do not hold a grudge. If using consequences, they should be immediate and help the youngster/adult learn from the outburst—saying "I'm sorry," sending a note to say they are sorry.	Be aware of "hallway overstimulation"—especially before the school day begins. Have student enter the building at a less popular entrance. If possible, have arrival time be 5–10 min after school starts. Dismiss early. Start the day off on the right foot by allowing time to go over the schedule for the day and work through any changes there may be. Putting the new schedule in writing often helps to decrease anxiety. At the start of the day, set daily goals *with* the student. Limit to no more than 3. Communicate behaviors *you wish to see*. Make it a cooperative task that provides concrete behavior expectations. Put goals in writing. Avoid the word "Don't," focus on the word "will" (e.g., "I *will* talk in a quiet voice" instead of "Don't yell."—"When I feel frustrated, I *will* tell Mr. Smith or another adult.") Provide positive attention and praise when student is maintaining control, especially in difficult situations. Celebrate success! Encourage communication and acknowledging feelings. Words are important—Listen carefully! Include the student in behavior plans. Having their input elicits cooperation and a sense of support. Be a role model: "I always say 'darn' when I am angry. Let's try that for you … darn, darn, darn." Practice when the student is *not* agitated or angry. Depending on the student and the situation, use humor. It is often effective. Anticipate build-up of frustrations and help him/her to remove self to "safe area." Create a key word or phrase that will alert the student that it is time to go. Practice using these words/phrases when the student is calm. Develop a plan and teach the student *what to do* if he/she feels angry or frustrated. Many students substitute a means of releasing this pent-up anger—long walks/ exercise, ripping paper, tearing rags, popping packaging bubbles. *Do not try reasoning when the student is out of control. Limit discussion.* Have a plan in place if student becomes more violent. Safety for all is a priority. Consistency in approach is imperative. Provide positive closure. Do not hold a grudge. If using consequences, they should be immediate and help the student learn from the outburst—saying "I'm sorry," sending a note to say they are sorry.

Table 12.4 (continued)

Common behavior characteristics in youngsters and adults with PWS	Possible management strategies	
	Home	School or workplace
Food-related behaviors and dietary restrictions For people with PWS, the message of fullness never reaches the brain— they are always hungry. In addition to this craving for food, food is metabolized at such a slow rate that it causes extraordinary weight gain. Food must be monitored, and the individual supervised at all times.	Make sure access to food is restricted. This may require locked pantries, refrigerators, kitchen doors, and garbage cans. Educate and inform *all family members, neighbors, and friends* regarding the restricted dietary needs. Be aware of the many "tricks" the person may develop to get extra food beyond that dictated by his/her diet and be alert for the many clever hiding places he/she may develop to store "illicit" food items. Supervise in kitchen, dining room, and in all food-related areas. Avoid providing the youngster or adult with money beyond that for a singular item for which he/she may be shopping (under supervision). Lock up all sources of money, including purses. Money buys food! Address privately any stealing or trading of food. Provide guidelines to school for treats or eating of extra food. Communication with all in school is very important. Follow a calorie-controlled diet. If a special calorie diet is needed and served by the school, a prescription must be obtained from a health care provider and should be a part of the student's educational plan. Do not delay snack or lunch; if this is necessary discuss ahead. Limit availability and visibility of food. Be aware of candy dishes and other sources of food. Praise situations where the individual does not take food when you see they could have. Praise does *not*, however, override PWS's hyperphagic drive to take available food. Do not use food as a reward or incentive. Be aware of smells—there is nothing like the smell of popcorn to make a person with PWS agitated. When going on a family outing, discuss all food-related issues *ahead of time*. Will you bring snack along or will it be purchased? If purchased, what will it be? Will the outing interfere with the time of a meal or snack? Provide supervision at large family get-togethers so that difficulties are avoided. Obtain weekly weight if indicated. Daily exercise should be a part of student's schedule.	Make sure lunch is placed with a bus driver or an assistant on the ride to school. Educate and inform *all people* working with this student, including bus drivers, custodians, secretaries, and volunteers. If the student states he/she has not had breakfast or lunch, call parents or caregiver before giving more food. (Oftentimes they say this to get more food.) Supervise in lunchroom and in all possible areas where food exists–including vending machine areas, trash cans on the playground and in restrooms, etc. In some cases, the student may need to eat in the classroom (with a peer/friend). Many always require supervision in hallways or near unlocked lockers. Avoid allowing the student to have money. Lock up all sources of money, including purses. Money buys food! Address privately any stealing or trading of food. Follow guidelines for treats or eating of extra food. Communication with home is very important. Inform parents if unauthorized food was consumed so that they may reduce calories. Follow calorie-controlled diet. If a special calorie diet is needed and served by the school, a prescription must be obtained from a health care provider and should be a part of the student's educational plan. Do not delay snack or lunch; if this is necessary discuss ahead. Limit availability and visibility of food. Be aware of candy dishes and other sources of food. Praise situations where the student does not take food when you see they could have. Praise does *not*, however, override PWS's hyperphagic drive to take available food. Do not use food as a reward or incentive. Be aware of smells—there is nothing like the smell of popcorn to make a student with PWS anxious and agitated. When going on a field trip or other outing, discuss all food-related issues *ahead of time*. Will you bring snack along or will it be purchased? If purchased, what will it be? Will the outing interfere with the time of a meal or snack? Obtain weekly weight by school nurse if indicated. Daily exercise should be a part of the student's schedule.

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Table 12.4 (continued)

Common behavior characteristics in youngsters and adults with PWS	Possible management strategies	
	Home	School or workplace
Poor stamina and poor motivation Low muscle tone and low motivation often present problems with going places, engaging in necessary exercise, or trying new things.	Get the individual up and moving. Send on errand. Take a walk. Use the strategy, "Lead like a Mamma Duck." Do not wait for the person with PWS to initiate movement. Move your body first and "pull" the individual to follow you. Move slowly and occupy yourself with other thigs if necessary. Do not look back to see if they are following and do not give eye contact. Start new activities by participating alongside the individual. Encourage and praise. Develop a reward system with stickers or special time with someone.	Get person up and moving. Send on errand. Take a walk. Start new activities by participating alongside the individual. Encourage and praise. Develop a reward system with stickers, special time with a teacher/aide, being the line leader, etc. Allow a student to earn the privilege to be a "special helper", for example, taking papers to the office (with supervision).
Poor energy People with PWS tire more easily and may fall asleep during the day despite adequate sleep at night. Narcolepsy is common in PWS, especially when the individual is sedentary for a period of time. Morning is typically their optimal performance time, when energy level is highest.	Schedule high energy, mobilizing activity before lunch or snack. Offer items/activities which stimulate large muscles and deep breathing——balloon blowing, party blowers. Provide scheduled rest time or a quieter activity if needed.	Schedule high energy, mobilizing activity before lunch or snack. Offer items/activities which stimulate large muscles and deep breathing—balloon blowing, party blowers. Provide scheduled rest time or a quieter activity if needed.
Scratching and skin picking These two behaviors are often seen in individuals with PWS and may be worse during times of stress or boredom. Combined with a higher pain threshold, these behaviors can result in tissue damage if not controlled.	Use diversion—provide activities to keep hands busy (coloring, computer time, play dough, hand-held games). Keep nails short. Apply lotion liberally—it keeps skin slippery. Skin that is soft and moisturized is more difficult to pick. Applying lotion can also be an effective diversion. Provide supervision. Cover area with bandage or similar covering. Do not just tell the individual to stop picking—it will not work. Apply mosquito repellant before any walks or outside activity.	Use diversion—provide activities to keep hands busy (coloring, computer time, play dough, hand-held games). Keep nails short. Apply lotion be liberally—it keeps skin slippery. Skin that is soft and moisturized is more difficult to pick. Applying lotion can also be an effective diversion. Provide supervision. Cover area with bandage. Do not just tell the student to stop picking—it will not work. Apply mosquito repellant before any walks or outside activity.
Difficulty with peer and other social interactions While people with PWS want, need, and value friends, they often have difficulty with social interactions. It may also be difficult for them to be exposed to the unpredictability of others for long periods. The need for order often translates into fairness issues and comparing themselves to others, often resulting in anger.	Many do better in small groups and at times alone. Pre-plan outings. Keep time short. Provide "supported" social outings, planned activities with a friend. Include child in planning activities that are of interest to him/her (board games, puzzles, computer games). Provide social skills classes that emphasize sharing, taking turns.	Many do better in small groups and at times alone. Pre-plan outings. Keep time short. Provide "supported" recess or social outings, planned activities with a friend. Include child in planning activities that are of interest to him/her (board games, puzzles, computer games). Provide social skills classes that emphasize sharing, taking turns.

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13 Educational and Social Issues for Adolescents with Prader-Willi Syndrome

Barbara J. Goff

It is All About Change

The transitions from elementary school to middle school and then again to high school pose dramatic changes for any student. The safety and security of being in a single classroom in a familiar building with the same teacher for at least one, possibly several years is suddenly taken away. Classmates who have been together for many years are dispersed. For some students, this provides an exciting opportunity to try out new behaviors and put on a more grown-up persona. For many others, it can be the start of a special kind of loneliness and rejection. This is especially true for students with significant cognitive and social deficits such as those with Prader-Willi syndrome (PWS).

It is not unusual for a student with PWS to be several academic grade levels behind their same-age peers. This may not have been a significant problem during elementary school placements, where there was a single teacher who knew the student's capabilities in all areas and could adapt the environment and curriculum accordingly. However, by middle school the social gap between the student with Prader-Willi syndrome and their classmates also has widened significantly as peer relationships now require a level of sophistication and savvy that may be beyond the capability of the student with PWS.

Paraprofessional Support For many, an additional significant change involves the loss of the one-to-one paraprofessional (often termed either a para or an aide) assigned to them for a good part of their elementary school years. In some cases, the student has had the same person serving as their para for several years, something parents hope for and support. If the aide support has been appropriate, the student has likely developed a degree of security with the aide both academically and emotionally which has helped support the student's success thus far. Aides who "hover" too closely to the student with PWS can inhibit other students' natural or spontaneous interactions with that student because of the constant presence of an adult, resulting in reduced opportunities for peers to serve as natural supports or even as friends. To minimize this potential, paraprofessionals must be guided on how to safely observe the student with PWS from a distance, how to facilitate social interactions with other students, and how to operate "undercover" as the "classroom aide" to provide academic support to *all* students in addition to the student with PWS.

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The transition to middle school is a natural time to re-evaluate a para's purpose. Is it for academic or behavior support or both? Is it to ensure that the individual does not access food throughout the day? Parents of a student with PWS reasonably fear that without the constant support of a 1:1 aide, their child might fall behind academically or engage in unsafe behavior toward himself (e.g., steal food, pick skin, leave the school site) or others (aggressive behavior). If these concerns are no longer relevant to the student, the continued use of a 1:1 aide at all times should be carefully reconsidered.

Research not specific to Prader-Willi syndrome suggests that assigning a 1:1 aide may impede independence in areas in which the child is capable [9]. Further, if the aide became an unintentional barrier to peer relationships in the earlier years, this barrier could become more difficult to negotiate during the teen years. As one parent pointed out, the adult world does not provide that kind of support and, for her son, that made for a very difficult transition upon leaving school. These arguments do not apply to most students with PWS; however, the hyperphagia symptom in and of itself requires a lifetime of supervisory supports, and neurologic symptoms that include deficits in frustration tolerance, emotional regulation, impulse control, and executive function skills interfere with the development and/or sustainability of peer relationships for almost all students. "Weaning off" supports that have been successful for the student with PWS is generally not recommended without irrefutable evidence that the current level of supports is no longer necessary to ensure the student's *future* health and safety and academic and social success. Should the student with PWS require continued constant support, assigning two or more paras throughout the day may help prepare the student for the reality of multiple teachers in middle and high school.

Classroom Placement Options The student placed in an inclusive program may be involved with several new teachers and different groups of students in each class. Each teacher has his or her own style, expectations and, perhaps, beliefs about the student with PWS. Most, if not all, will have had no prior experience working with students with PWS; further, they will not have the luxury of getting to know the student every day, all day. Thus, a great deal of collaboration and contact between school and home must occur on a routine basis.

Students placed in self-contained classrooms have a greater possibility of being with one or two familiar classmates from earlier grades. Typically, in this setting, there is one teacher with one or more paraprofessional aides. Physical transitions are fewer, and a consistent routine is more easily established while also allowing for greater flexibility in meeting individual needs.

Some students may transfer to a special middle or high school for students with significant learning disabilities. Here, too, staff need to be prepared to work with the student with PWS. The student, on the other hand, may need reassurance that the change in placement is not a failure, but an opportunity for a safer and more appropriate learning environment as well as a place to make new friends.

New People and Places No matter the placement selected for the student with PWS, it is probable that most if not all administrative, teaching, clinical, and support staff will be unfamiliar to the student and will require the establishment of new relationships. Further, all who will now interact with the student throughout the day may have a great deal to learn about the student as a person as well as the special characteristics of that student related to having PWS. A replay of the mistakes and misunderstandings of the earlier years may occur as the staff progresses along the learning curve. Parents and caregivers, once again, must consider and plan for how this learning and relationship-building will occur. The goal is to minimize the possibilities of their child (and themselves) being unfairly criticized, inappropriately managed, and painfully misunderstood. Parent or PWS association-led educational training session(s) held at the start of every school year that include everyone with whom the student will interact—principal, vice principals, teachers, aides, counselors, librarian, nurse, caf-

eteria staff, janitors, and bus drivers —are highly recommended.

Moving from classroom to classroom throughout the day poses a special challenge for many individuals with PWS. The new building is probably much larger than the previous school building; locations of the various classrooms and offices must be learned, as well as how to access lockers. Further, changing classes means moving quickly from room to room so as not to be tardy. This requires planning and organization of materials needed for each class; both areas of weakness for individuals with PWS. Many students with PWS need permanent permission to leave a class early or to arrive to a class late.

Larger buildings also mean more available and unprotected food sources; hence, increased stress. It also means bigger and more chaotic cafeterias with food service staff that are unfamiliar with the biological food drives of a student with PWS. Such an open environment requires the student with PWS to resist many opportunities to obtain food (e.g., open lockers, offices, trash cans, snack machines). The range and constancy of these demands present significant challenges for the person with Prader-Willi syndrome: challenges that should not be underestimated.

Transportation Transportation to and from school will also be affected. There may be a new driver and bus monitor, new children on the bus, a new route, and a different pick-up and drop-off time. This change alone can be very stressful for the student with Prader-Willi syndrome and should be considered when designing transition plans. Transportation personnel are often left out of training opportunities and, therefore, resort to their usual methods for gaining compliance for expected bus behavior. Frequently, these methods involve inducing good behavior by offering the child edible treats, or, equally problematic, making some kind of verbal threat for misbehavior. The latter approach is contraindicated for the student with PWS and almost guarantees increased, possibly dangerous misbehavior on the bus, or refusal to ride the bus at all. It is important that transportation personnel receive training specific to the child with PWS in order to increase the likelihood of a positive and safe start and end to the school day. Too frequently, this training is left to the parents; although, over time, school personnel usually develop a relationship with the drivers and aides and readily contribute to ensuring safe and problem-free bus rides.

The time spent traveling to and from school is often one of the most problem-laden and yet, one of the most ignored. Parents often report issues in getting their child on the bus in the morning while school staff complain about difficulty getting them off the bus upon arrival at school and back on the bus for the return home. It sometimes seems that the only problem-free transportation time is when the child gets off the bus when delivered home at the end of the day.

Food/Nutrition As indicated, larger schools have a greater number of food sources available. Middle and high school cafeterias often provide numerous snack choices, in addition to a relatively wholesome school lunch. Often available are soda, bagels, chips, and candy, as well as a variety of dessert options. Snack and soda machines also are available and often are scattered throughout the school building. The typically developing adolescent does not choose to spend money on the school lunch (unless it is pizza), opting *instead* for soda and snack foods. Unless closely supervised, individuals with PWS will choose the school lunch *in addition to* the soda, snacks, and desserts. Recent research suggests that individuals with PWS are more likely to choose a larger quantity of a less-preferred food over a lesser quantity of a more preferred food [10]. Incorporating this finding into a strategy offers an opportunity for the student's caretaker or cafeteria worker to promote healthy choices, such as offering *extra* vegetables as an alternative to a *lesser* quantity of macaroni and cheese.

There are numerous additional opportunities throughout the school day for food to be obtained. Food sources within the classroom include but are not limited to: a teacher's stash in her desk (and the cups of coffee, tea, and other liquids that are consumed throughout the day and left sitting out); students' desks, backpacks, unsecured

lunches; trash receptacles; and the supply of snacks in the classroom closet. Even more opportunities are available outside of the classroom: cafeteria (including packets of condiments often left out for self-serve), unlocked lockers, coat pockets, meeting rooms and offices, hallway floors, bake and candy sales, special events, and friends who may be all too willing to share or bargain. Creating a completely food-free environment in middle and high school settings is nearly impossible; thus, monitoring access to food is often the primary function of an aide. There is no doubt that, as the student's social world expands, so too does their exposure and opportunities to access food. Therefore, it is imperative that educators and parents collaborate on strategies to create a food secure environment to the greatest extent possible.

Many special education curricula provide classes in life skills which include food preparation and cooking. Of course, the student with PWS wants to participate in these classes, but few can manage the stress and temptation of such close proximity to food. Even those who can participate without stealing food are most likely experiencing a high level of anxiety, albeit unseen by others. Parents and school staff must work together to determine if participation is appropriate and, if not, decide upon a meaningful alternative. In lieu of a cooking class, a more practical life skill might be instruction in nutrition and healthy choices, as that knowledge would allow the person to engage in decision-making about their diet and nutritional needs throughout their lifetime. It should be noted that the dietary needs of persons with PWS are somewhat different from those of same-age peers; therefore, instruction should be modified accordingly just as it would be for a child with diabetes or other medical condition. Until a medication that modifies the impact of hyperphagia is developed, most people with PWS are unlikely ever to have unrestricted access to food; however, they should be empowered through knowledge to have input into their menu plans as they move into adulthood.

Culture For many children with PWS, entering middle and high school is pure culture shock. Elementary school is often a much smaller, kinder, gentler place where the student has spent the last 5 or 6 years. Prior to the transition, the student is at the top of the student hierarchy. With the transition, the student is now at the bottom of the heap and everyone around is older, bigger, louder, faster, and, in some cases, meaner. Moreover, this may be the student's first exposure to frequently unchecked, inappropriate, and unacceptable teenage behavior that is outside previous experiences and comfort zones. Suddenly the happy kid who loved school and all his teachers and friends has a significant increase in anxiety resulting in outbursts and perhaps other behaviors that may have existed but were manageable in elementary school. They may come home and "let loose" in a way never seen before. Parents report that when checking in with the school, the report is that the child "had a good day." How could that be? What is happening to cause this behavior?

Students are swearing, pushing, kissing, hugging, fighting, yelling, talking back to teachers, teasing each other mercilessly, using sarcasm incessantly, conversing with slang expressions that makes no sense, and talking about things of which the student with PWS may have no awareness. The resulting internal experience may be total chaos. Given that students with PWS rely on structure and sameness with rules and boundaries, suddenly the environment of middle and high schools feels as if one is in a world with little of that. This may become sufficiently overwhelming that reactive behavior episodes result.

To illustrate, a family reported their son was in jeopardy of losing his placement in a mixed program of general and special education classes at his local high school. He had been doing well academically and behaviorally with the usual PWS glitches along the way necessitating lots of support. His mother indicated "Elementary school was very nurturing with wonderful teachers and aides. Middle school was difficult, but high school was a nightmare." Suddenly, her son was coming home extremely distraught. His anxiety, already high, went through the roof. No one could explain the dramatic change, nor suggest a remedy. His parents tried to help the high school

personnel to understand that part of the difficulty was that food was everywhere and that such availability is a "set up" for a person with PWS who knows he should not take food that is not his, but just cannot help it. This mother indicated that multiple teachers would leave bowls of candy on their desks. The impact of such an environment was vividly illustrated the day the school called the family to report that they could not find their son. His dad told them, "Look for the nearest classroom that is unlocked, not in use, and has candy on the teacher's desk." "Bingo." Further, there were the classmates who felt sorry for the student and shared their lunches. Over and over the parents explained to school personnel the need for these issues to be addressed for their son to function; school staff would listen and nod their heads, but nothing changed. This mother concluded by reporting, "I still remember you (the author) telling us after a consultation that you couldn't believe he lasted as long as he did before he had a psychotic break. Inclusion may work for parts of school, but I really believe it sets our kids up for much more stress and failure."

This episode highlights additional stresses for the student with PWS in what for them is an open, unprotected environment, stresses beyond easy access to food. In recounting their son's attempt to cope with the transition into the high school environment, these parents described how their son would carry the high school rule book with him throughout the day. Rules matter to people with PWS; rules make the world more manageable and reduce anxiety. To persons with PWS, breaking rules is a serious matter requiring swift and significant consequences. In this young man's experience, he was witnessing constant unaddressed infractions of the rules each and every day as he walked the halls of his very large high school and sat in his classes! Eventually, he experienced a psychotic episode requiring hospitalization. The cumulative effect of all the expected stressors of high school along with the chaotic and unruly teenage culture exceeded his ability to adjust and cope. For many individuals with PWS, it is not just difficulty with change and transition itself, it also may be the experience of being thrown into and expected to navigate an entirely new world with a different language, values, and behaviors for which they are unprepared.

In general, students with PWS experience increased stress and anxiety when facing the many changes and challenges that accompany adolescence, and these feelings are sometimes manifested in unacceptable ways. For example, the student may be "in trouble" more often than was previously the case, resulting in increased phone calls from the school to parents asking for the student to be removed for the day. In some instances, the school may decide that it can no longer serve the student within its existing programs and will recommend placement in a special class or school for students with behavior difficulties. Such placements have not proven to be successful for the student with PWS as much of what gets labeled as behavior problems (based on diagnostic criteria for neurotypical students) actually are features of the syndrome that need to be recognized as such and managed accordingly. Schools for children and adolescents with diagnosed behavior disorders utilize intervention strategies aimed at returning the student to a less restrictive program. These strategies assume that behavior can be substantially altered using traditional behavior modification and management approaches. Since most of these strategies are ineffective without consideration of the unique neurological and behavioral phenotype associated with PWS, placement in traditional programs for students with behavior disorders often results in worsened rather than improved behavior. Programs utilizing environmental modifications and a variety of situation-specific preventative strategies are most effective for managing PWS-related behaviors. Strategies utilizing the consequence approach (positive and negative reinforcement and punishment), no matter how powerful (e.g., the use of food)—cannot override the neurological drives inherent in the syndrome and are never recommended. With these background caveats in mind, let us consider some transition strategies for supporting the student with PWS as they move on to middle and high school.

Transition to Middle or High School: Paving the Way

The most important strategy for an educator is to "be prepared." Training and support in working with the student with Prader-Willi syndrome should be the priority for middle or high school personnel unfamiliar with the affected student's special needs. Parents may need some additional support as well. When all people who work with the student with PWS are informed and environmental concerns have been addressed, there is a greater chance for a positive learning experience to occur. Additional strategies include the following:

- The student's multidisciplinary team, including the parents or guardians, should meet as early as possible in the school year prior to the planned transition in order to identify the specific program and services the student may need, and to develop a transition plan.
- If a change to an entirely new program (e.g., substantially separate vs. inclusion) or school is necessary, both parents and school personnel should visit to ascertain the fit between the program's services and the student's needs. One criterion for future success is that the new program or school demonstrates openness to learning about Prader-Willi syndrome from previous teachers, parents, and experts in the field.
- Once a program and setting are determined, the student and family should tour the building (take pictures!), learn where their child's primary classroom will be located, and meet with the teachers, administrators, and clinical staff. If the student will have more than one teacher, a key teacher who will be the decision-maker and primary communicator should be identified. A regular and user-friendly communication system between other school personnel and the key teacher, and between the key teacher and the family or caregivers, should be established. For caregivers, e-mail may be preferable to sending a notebook back and forth in order to prevent the student from ripping out pages or "losing" the notebook.
- It is useful for the parents to develop a written introduction to their child which describes those characteristics of PWS that their child exhibits and under what conditions. It should include any behavior management tips and tricks that have proven successful in school and home. It should also provide a brief description of the student's family make-up, personal strengths and interests, along with a few "fun facts" about the child's life experiences to date. This kind of information will provide teachers with a positive picture of the student and a way to connect with the student early on.
- The daily schedule (if known), especially the snack and lunch schedule, as well as where food will be eaten, should be reviewed with the student. Whenever possible, less preferred activities or classes should be followed by more preferred activities or classes. In that way, the schedule itself serves as a motivator for the student to accomplish what is expected so the more rewarding activity can occur.
- Similarly, school or classroom policies or procedures impacting the student (e.g., code of conduct, dress codes, and behavior management programs) should be reviewed ahead of time to determine if there are any items that might be problematic for the student. One typical example is homework. Homework for the student with PWS often becomes hours-long nightmare for the entire family. Substantial homework is often expected in the upper grades; hence, a discussion should take place about what reasonably can be expected of the student (and family). If the student takes issue with specific policies or procedures, a meeting with the principal to review them often resolves the problem. Individuals with PWS recognize and appreciate the power of authority figures and who has the "final say."
- If the student has a behavior support plan, it should be carefully reviewed and revised to reflect the new setting. Data on behaviors once the school year begins should be taken in order to identify and address any new or changed behaviors in the new setting.

- Environmental changes that need to be made prior to the school year should be determined and a plan for their implementation developed. For example, is food kept in classrooms? Where are lunches and snacks kept? Where are trash receptacles located and do they have lids? Are any of the classrooms located close to the cafeteria where the scent of food being prepared is evident? Should the student eat in the cafeteria, and if so, what degree of supervision is needed? If they will not be eating in the cafeteria, what arrangements can be made to ensure that lunch time includes socialization with a peer? If there is a food preparation component to any of the student's classes, how will this be managed while considering the needs and abilities of the student? How will special events involving food be handled?
- Does the student need an adapted physical education program? Will there be opportunities for the student to engage in physical activity beyond the one time per week (if that) in a physical education class?
- Are there any extracurricular activities that would be appropriate for the student? Is adult support needed to participate in these activities? Would special transportation be required?
- How and when will the transportation staff, especially the driver and bus assistant/monitor, be educated about PWS and the specific child they are transporting?
- It is often helpful for the student to view pictures of school personnel prior to starting the school year, particularly if the student is very anxious. Therefore, caregivers may want to photograph the school, the assigned classroom, and the key teacher(s). This way, over the summer months, caregivers can use visuals to review what and where various classes and activities will be happening, and with whom.
- Finally, assuming all the basics are in place for the next school year, it is advisable to set up a time in the fall for a formal training session with a PWS specialist.
- For some students, scheduling such training before the start of school is preferable, while for others there may be an advantage to wait until after the student has been in the new program for a few weeks, after the school personnel have gotten to know the student so that the training will then have more meaning and student-specific questions can be addressed. It should be noted, however, that changing routines and rules after they have been initiated can be quite difficult for most students with PWS and may result in unwanted behaviors.

PWS-Driven Behavior Challenges

The typical characteristics associated with PWS persist throughout adolescence. Although not universal, certain behavioral characteristics such as hoarding and skin picking often become progressively worse as the child moves into the teen years [7]. Some caretakers report increased skills, abilities, and creativity in obtaining food and other desired items or activities. It is not unusual to hear parents and teachers report that the adolescent is suddenly doing all kinds of food seeking never before attempted. Temper tantrums and "shutdowns" that may have occurred sporadically throughout elementary school now escalate in response to greater academic demands and challenging social expectations. Most individuals with PWS (75–90%) exhibit acting-out behaviors, including temper tantrums, impulsivity, aggression, and stubbornness to a greater degree and with greater intensity than individuals with equivalent intellectual challenges from other etiologies [3, 7].

The student's weight may also affect behaviors, particularly maladaptive behaviors and even mood disorders. Research suggests that those individuals with PWS who are thinner demonstrate more maladaptive behaviors than those who are heavier [5, 6, 17]. While many perceive that individuals with higher IQs have greater and more severe maladaptive behaviors, the evidence suggests no significant differences based on IQ [6]. However, there is a relationship between genotype and psychiatric conditions with individuals with the uniparental disomy (UPD) type being more likely (predisposed) to have a

psychiatric diagnosis at some point in adolescence or adulthood [15].

In addition, PWS individuals, like many others with intellectual disabilities, exhibit impaired executive functioning. Executive functioning involves a range of mental skills including flexible thinking, self-control, working memory, and a variety of other skills essential for managing daily life. Without these, life for the adolescent is extremely challenging as they try to negotiate the complexity of the teenage world. For instance, a student with PWS may be able to "tell" time (i.e., can accurately read an analog clock or digital watch), but may not understand the concept of time (as in being able to plan how much can be accomplished within 30 min). Sequential planning is also an area of difficulty, so laying out the steps of a project over time can be extremely difficult. Multiple repetitions and direct instruction are required for skill acquisition. Flexible thinking, the ability to "shift gears," while a critical life and learning skill, seems almost nonexistent in people with PWS, yet is routinely expected of them in middle and high school. Working, or short-term, memory is also impaired so the skill that appears to be mastered on Wednesday may not be demonstrated on Thursday, which is then attributed to resistance on the part of the student. The student is pressured to perform, becomes frustrated and acts out in some way. A "behavior problem" has been born! The effects of these deficits in executive functioning are significant in determining instructional as well as behavior strategies.

Since there is a great deal of individual variation in behavior among people with PWS, supports and interventions need to be person specific. This necessitates involving the interdisciplinary team including the family and the individual to the extent possible. Behavior management strategies must take a different shape in the adolescent and young adult years and must include an increasing emphasis on self-awareness and self-monitoring. Sticker charts and verbal praise alone may no longer be adequate to achieve desired outcomes. A behavior support plan will have far more success if the student has a voice in its development. Thus, one needed focus is on the individual's recognition of their problematic behaviors and an agreement to change them. A common example would be skin picking. Currently there is no universally effective cure, nor is it clear the extent to which individuals can control the urge. But the likelihood of redirecting the individual when the behavior occurs is enhanced when the person has recognized picking as a problem and wants to address it. For this reason, behavior contracts are generally a more effective strategy than sticker charts for the older child and adolescent. As with all teenagers, students with PWS react very negatively to any perceived condescension. There must be a *genuine* foundation of respect and appropriate levels of involvement to ensure the maximum effectiveness of any behavioral strategies. While for many teenagers with and without PWS, a targeted behavior program can assist with modulating excessive behaviors; others may require ongoing counseling or other forms of support, including medication as a last resort.

For all behaviors, environmental management is essential. Specific behavioral "triggers" need to be identified and eliminated. For example, skin-picking frequency increases when the student is watching videos or is unable to comprehend the presented material. Knowing this, antecedent interventions can be developed. Having visible food in the classroom, or even just knowing there is food in a locked classroom cupboard, is a major distracter from learning as the student will focus on how to access the food, not the lesson. Removing all food from a classroom is a simple environmental modification that has a direct and positive effect on learning and behavior for the student with PWS. There are likely numerous other triggers for students with PWS that may or may not be food related. These are best identified and addressed with family and other experts who are familiar with the child and the behaviors associated with the syndrome. It is well documented that behavior support programs based on antecedent control are likely to be much more effective than those primarily based on the application of consequences (positive, negative, or punishment).

Fitting in: The Adolescent Struggle

The social success of a typically developing adolescent depends, in large measure, on how well they can follow fashion, music, sports, movies, and other leisure time trends, how well they speak the language of adolescence (a language for which most parents require translation) and can take part in both casual banter and serious conversations on topics of the day. As a pre-teen and teen, the ability to relate to a variety of people, from peers to principals, is an essential skill. A typically developing adolescent is learning to manage their feelings and responses to frustration and anger and to *read* social cues in order to avoid saying or doing something grossly inappropriate according to teenage standards. In short, typical adolescence constitutes a complex society with its own culture, language, beliefs, and expectations, much of which is at variance with the upbringing of the child with PWS.

Students with disabilities including those with PWS are often excluded from the social grouping that occurs in middle and high school. When this happens, the student may not understand why classmates are distancing themselves both physically and socially from them, or even teasing or bullying them; however, they certainly know it is happening and suffer as a result. Some may try even harder to be part of a social group causing their families to fear their child will be even further rejected or, worse yet, find acceptance with undesirable companions either at school, in the community or, as is often the case today, through social media. While some students with PWS express their negative feelings by acting out, others may withdraw and suffer with depression. Parents should be vigilant for any of these possibilities so they can intervene early on. All too often the feelings and experiences of people with intellectual disabilities are minimized or discounted altogether, leaving the individual increasingly vulnerable to behavioral and mental health issues.

Social cognition or the ability to read and understand social cues in a situation and act accordingly has been identified by several researchers as a functional deficit for those with PWS, particularly among those with UPD [4, 8, 18]. All human beings rely on a variety of verbal and nonverbal cues to understand and interpret the meaning of any situation. People with PWS have a significant weakness in identifying both vocal and facial cues [16]. Further, when there are more than just a few people involved in a social situation, the ability to focus on relevant cues is markedly reduced. The previously described deficits in executive functioning further impact the ability to self-monitor, detect, understand, and respect another's point of view while self-regulating emotion [1]. These areas of weakness make it difficult not only to manage academics but also impact the ability to successfully negotiate the social challenges that accompany adolescence. The implications of this are far-reaching when it comes to "fitting in." Clearly, middle and high school can be fraught with peril for the student with PWS.

There are many students with social skills deficits who have disabilities other than Prader-Willi syndrome. They may be students with learning or emotional problems, sensory or neurological impairments, or students with medical disorders or physical disabilities. This constitutes a large population of students who would benefit from formal social skills training.

The most effective social skills training occurs in small groups with students meeting (at least) weekly throughout the school year, facilitated by an adult proficient in social skills training [11, 13]. In this setting, the group can practice many practical skills such as listening, using good manners, planning, asking someone out for a date, expressing anger and frustration, and solving a variety of everyday problems, as well as learning relaxation techniques.

Role-play is particularly useful. Students are given situations to act out, first with inappropriate behaviors yielding negative outcomes to be critiqued by the group, and then with appropriate behaviors producing desired outcomes. Supplemental videotaping provides a powerful training tool, especially for students with PWS

who are predominantly visual learners. Students, including those who participated in the role-play, can see themselves as others see them and critique their own behavior, both positively and negatively, making the role-play situation more realistic. It is also important to create situations that mimic real life. For example, a student may want to learn how to channel his anger, join a club, ask a friend to go to a dance, or even how to dance!

Targeted intervention directed not only toward improving social skills but also directed toward improving both executive functioning and social cognition can strengthen these areas of weakness. And, for individuals with PWS, these skills are equally, or perhaps, more important than reading, writing, and arithmetic. It is not unusual to see a social skills goal in a student's IEP; rarely are the interventions designed to enhance the more complex deficits in executive functioning and social cognition. While this work should begin in elementary school, it is essential to address these skill deficits throughout middle and high school. The implications of this are far-reaching when it comes to "fitting in."

As is true for all teens, adolescence also is a period of severe self-criticism and self-consciousness for students with PWS. In addition to an increase in difficult behaviors at school and home, a student may, for the first time, express a desire to quit school or even commit suicide. While both eventualities are unlikely, such expressions of distress are not uncommon, and cannot be ignored. All increases in frequency and severity of behavior problems (whether inwardly or outwardly directed) are pleas for help and should be recognized and responded to as such.

Several factors should be considered in supporting the adolescent with PWS. One largely ignored area of research has been the self-image of young people with PWS, specifically, how they perceive their physical selves. In a small study on PWS and self-image involving 43 males and females, a Figure Rating Scale asked the participants to rate themselves on how they thought they looked and how they wished they looked [12]. The findings revealed significant discrepancies between how they thought they looked and how they wanted to look; even to a slightly greater degree than those in the general population. Not surprisingly, females reported greater body dissatisfaction than males, with greater dissatisfaction correlating with a higher body mass index. As a result of early diagnosis, growth hormone, and immediate efforts at weight management, many students with PWS never become obese and enter school at a healthy weight, but this is not true for all. This study also raises the question as to what other observable physical characteristics might be seen negatively by those with PWS: height, breast or penis size, skin blemishes resulting from skin-picking, voice changes, facial and body hair? These are all stressful areas for typical teens. But since individuals with PWS often have cognitive deficits, it is assumed that they are unaware or dismissive of their appearance. While this may be true of some individuals with more severe cognitive deficits, it is not the case for most individuals with PWS who have IQs in the mild to borderline/average range.

Adolescent Friendships and the "S" Word Young people with PWS want what most teens want—friends and a close relationship with another. They can carry this desire to extreme lengths in their search for a special friend, including obsessing over a particular individual (sometimes a favorite adult). Dating and romantic relationships are another area where adolescents with PWS need education and guidance. Phone calls and texting etiquette needs to be taught. Excessive and often inappropriate use of the phone can become a daily problem. Rules and guidelines may be needed that outline when and where public displays of affection can take place. Many need to learn what should be said and done to make sure consent is obtained. It is recommended to use this consent approach for hand-holding, hugging, and other intimate situations. Educators need to make sure they understand what their students are being told at home about acceptable behavior. If we rely on students with PWS to learn from their peers, they are likely to see and mimic inappropriate displays of affection. Some parents and providers have used writ-

ten contracts to outline specific dating or friendship behaviors, and when and how they are to be employed.

Sexuality is also part of social development, and, while individuals with PWS may or may not go through a complete puberty, they are still subject to sexual feelings and the desire to be romantically involved. Most schools provide health classes that describe the physical changes of adolescence; too often students with intellectual disabilities are excluded from these classes. For students with PWS, these changes may be minimal or nonexistent unless they are receiving hormone therapy. These differences are often a very sensitive area for affected individuals. Boys may want to know why they are not getting taller and more muscular, have an unusually small penis, are not developing facial hair, or experiencing a deepening of their voice. Girls want to know why they are not having a period and whether they can have babies. Teachers and caregivers must be prepared to deal with these issues in an honest, respectful, and sensitive manner. Collaboration between home and school is essential to convey information and advice in a consistent fashion. Given the unique characteristics of PWS, the health education instructor would need to understand that pubertal development does not follow the usual trajectory for adolescents with PWS in order to be better prepared to address the questions and concerns of these students. (Note: While reproduction is highly unlikely, it has happened in several documented cases of young women with PWS. See Chap. 21 for further discussion of sexuality issues).

Finally, many individuals with PWS are highly motivated to play the role of nurturer or caregiver. This characteristic allows opportunities to have the student assist others who may be younger or less capable (e.g., push a wheelchair, carry someone's knapsack, read to a young child, or oversee the classroom pet). There are endless opportunities to use the student's strengths and interests to build social skills. They should be considered when the student is transitioning to a new setting. Caring for others can be a big boost to one's self-esteem, a critical component of personal development and socialization.

Looking Ahead

Many parents and caregivers ask, "Is there life after graduation?" The answer is "Yes, but it must be carefully designed." The federal law, Individuals with Disabilities Education Act (IDEA), mandates that transition planning be initiated during the school year in which the student turns 16 years old. However, many school districts begin transition planning at age 14 or 15, which is strongly encouraged. With early planning, the high school program can be designed to support the individual's future goals. The student's strengths and needs can be assessed and considered in mapping out a path to adult life whether it includes continuing in an educational program, securing a job, or participating in a vocational or pre-vocational program. For some students, investigating residential options occurs at this time, especially since state waiting lists can be as long as 15 years or more for a PWS-specific setting. While the student is eligible to remain in school through the age of 21 or 22 (varies by state), not all will. Some may meet the requirements for a regular diploma and graduate with their class. Most students with PWS remain in school for as long as legally possible independent of whether they are working toward a regular diploma. This allows them to derive maximum benefit from available school-based programs. Many schools provide classes on a variety of work-related skills, such as filling out an application, how to have a successful interview, being on time, managing conflict with coworkers or supervisor, appropriate dress, and the importance of adhering to the policies and procedures of the workplace. Some schools also provide community-based vocational experiences whereby the student goes to a variety of workplaces, performs the duties of given jobs, and is evaluated on their work skills. Sometimes the school will facilitate and provide supervision for a volunteer experience when the individual feels strongly about a certain type of job. In the case of a student with PWS, volunteering at an animal shelter is often at the top of their list. All of these opportunities contribute to their understanding of work expectations in general, as well as the different types of

jobs they may want to consider or rule out for their future employment.

A more recent opportunity for individuals with developmental disabilities is participating in a dual enrollment program with a college or university. The program is called Inclusive Concurrent Enrollment (ICE) and is designed for the 18- to 21-year-old population who are not expecting to earn a regular diploma [2]. The students spend their days on a college campus with a support person from their school while auditing course(s); utilize the college resources such as the library, gym, dining hall; and engage with typical college students who have volunteered to be a mentor. While this opportunity ends when the student reaches the state's age limit for public education, it is an excellent preparation for being in a college environment post high school, making new friends, interacting with nondisabled students, learning how to be flexible, improving decision-making skills, and have an opportunity to mature in a way that would not be available in the more protective public schools' program. One program participant who also has PWS indicates "This is the first time I ever felt normal."

Some school districts have a transition specialist who works with the multidisciplinary team assessing the student's strengths, needs, and vocational interests. The high school curriculum can then be designed so that it addresses those areas, as well as identify community resources relevant to the student's goals. Table 13.1 gives an overview of the timetable for various transition activities and events during the adolescent education years.

Transitioning into the adult world is stressful for the individual and the family. The protections of IDEA no longer apply and there are no laws guaranteeing services for the student after they exit the school system. For most caregivers, and even school personnel, this comes as a surprise, and often too late to have the most comprehensive and thorough transition plan in place. There are many things to consider in planning for the future:

- If the student is capable of further education in either a 2-year college or specialized training program, how will it be paid for and who will monitor his access to food?
- If the student has proven capable of entering the world of competitive employment, who will assist them in locating a job and providing the necessary job coaching? How will access to food be managed?
- If the student requires a sheltered vocational placement, where does one exist? Is there a waiting list? Does the student meet eligibility requirements? Is the program, environment, and staffing compatible with the needs of the young adult with PWS? Is the program open to receiving training on the syndrome?
- Is a residential placement desired after high school? If so, what are the options? Does the student meet eligibility requirements? Is there a waiting list? What is the funding mechanism? If a PWS-designated residence is unavailable, are there openings in programs amenable to making significant environmental changes and to receive training about PWS?
- Are there other services for which the student is eligible: respite, recreation, case management, transportation, training, or educational programs? (Table 13.1).

Without early planning, the student with PWS may find themselves at home with no work or residential services.

To facilitate a smooth transition, one of the first services needed is that of case management, typically provided by a county or state agency or contracted out to a community-based agency to individuals with intellectual and developmental disabilities. The school district should provide this information. Case managers assist the student in linking with a variety of community resources for which they qualify. This can be a problem for individuals with PWS, since many exceed the IQ eligibility criterion (usually 70–75), and many states do not recognize developmental disabilities as a population they are mandated to serve. When this occurs, parents should reach out to experts in PWS to assist in making a case for services regardless of IQ. Support and resources can also be obtained from the national Prader-Willi Syndrome Association.

Table 13.1 Timetable for transition services: a guide for planning activities during the transition years in special education. Based on individualized programming, there may be great variation in scheduling from one student to another

	Ages 14–18	Ages 18–20	Ages 20–22
Academic	If mainstreamed, continue academic goals; may graduate at 18, which may cease special education services If in Special Day Class (SDC), include functional skills in goals	If mainstreamed and still in special education, continue academic goals If in SDC, continue mix of academic and functional skills goals	If mainstreamed, continue academic goals; determine use of post-secondary education and apply for funding and to post-secondary placements (junior college, trade school) If in SDC, deemphasize academics, increase focus on domestic and vocational functional skills
Domestic	Assess skills in personal hygiene, nutrition, cooking, household maintenance Build skills	Build skills	Continue to build skills using home, classroom, and community environments
Community	Assess skills in, interpersonal communication and relationships, use of community services	In community more frequently as learning skills	Continue to build skills in all domains in the environment in which those skills will be used
Vocational	Rehab counselor assigned, application made, with proof of disability and vocational potential School assesses vocational knowledge, interests, aptitudes, skills	Begin to meet/ interview vocational agency staff Gain a variety of work experiences and skills	Continue gaining work experience Select vocational agency, if wanted, to serve needs after leaving school
Site of educational activities	Classroom with some community-based exposure	Classroom Community Vocational sites	Classroom may be on junior college campus Community Vocational sites
Leaving school	Some choose to leave (drop out) with incomplete skills	Many of nondisabled friends have left school (graduated) and gone on to college, trade training, or work May graduate but continue studies	Will exit special education sometime during age 21, typically with certificate, not diploma

Source: Adapted from Seguin and Hodapp [14]

Service providers for adults, both residential and vocational, once identified, should be invited to team meetings well before the student is scheduled to leave school so they might describe the services they offer and how they are accessed. A note of caution is in order: The language of the adult service system is quite different from that spoken in education, so families and school staff should ask for translations. Again, families seeking residential services for their child should be made aware that residential programs specifically designated for people with PWS are scarce and may not even exist in their state, let alone community. The young adult may need to be on a waiting list while looking at other residential options. (See Chaps. 14, 15, and 16 for a more extensive discussion of these issues).

In short, early planning along with a great deal of collaboration between school and home is required to support the adolescent with PWS through the turbulent teens and into the next phase of their journey. Schools must provide relevant programs to prepare these students for an entirely new set of challenges. Parents must continue to advocate for their sons and daughters to obtain services which will ensure that

they have meaningful activities and needed supports to achieve their goals as young adults. The adult service system is generally not as "user friendly" as the educational system. There is no post high school equivalent of IDEA and while an individual may be eligible for a service, it does not guarantee that it will be made available. Schools need to support the parents as they prepare to enter this new world and parents, as is always the case, must continue their advocacy in securing needed services and programs for their child.

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14 Transition from Adolescence to Young Adulthood: The Special Case of Prader-Willi Syndrome

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Introduction

Transition to Adulthood for Individuals with Prader-Willi Syndrome For persons with or without disabilities in their late teens or early 20s, becoming an adult can be difficult. While one may desperately desire to leave their parents and live on their own, the realization of that dream becomes more complicated than earlier imagined. Getting a job, finding a place to live, becoming economically and emotionally self-sufficient, and establishing relationships with friends and significant others – all require actions that are not always readily apparent or easy to accomplish.

While possibly even more complicated for individuals with disabilities, the process of entering adulthood is aided by the special education system. Indeed, special education's overarching goal is to prepare students with disabilities for an adult life that is as independent as possible. From early intervention through secondary school, educators and families work together to develop educational programs that will help students with disabilities gain the academic and functional skills necessary to actively participate in their community. As youth near the end of their school years, families and members of the Individualized Education Program (IEP) team prepare students for life after high school. In special education, this movement from school to adulthood is commonly referred to as the transition process.

In this chapter, we describe this process for youth with Prader-Willi syndrome (PWS). We first describe the transition process as it applies to all youth with disabilities. We focus both on the context in which transition occurs – the many changes in service systems, in student and parent reactions, and other issues – and the areas or domains in which transition takes place. In the second section, we focus on transition issues specific to Prader-Willi syndrome, including behavioral and medical-physiological issues. Finally, we provide recommendations for a more successful transition process for adolescents and young adults with Prader-Willi syndrome.

Transition in Special Education: Context and Domains In its most general sense, transition refers to change. In special education, the term refers to the change or movement of adolescents

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with disabilities from secondary school to adulthood. This period is critical in that adolescents navigate biological and emotional changes and begin to plan for their futures – thinking about potential jobs, education or training opportunities, relationships (both platonic and romantic), and residential options.

Although these changes can be difficult for anyone, youth with disabilities and their families also need to manage changes in service delivery models. They need to understand transition requirements and services and the change from entitlement to eligibility-based services. It is also important to consider meaningful student and family involvement, common challenges faced by transition-aged youth with disabilities, and person-centered planning. In essence, then, transition relates to larger issues – which we will call the context of transition – and the specific domains in which transition occurs. In the pages that follow, we discuss each in turn.

The Context of Transition

IDEA: Transition Requirements Defining transition as "a coordinated set of activities for a child with a disability that is designed to be a results oriented process" (§300.43), the Individuals with Disabilities Education Act [1] mandates that schools must initiate transition planning before the student's 16th birthday (some states begin when the student turns 14). At this time, an Individualized Transition Plan (ITP) is created for every student with an existing IEP. The ITP is a document that outlines a student's post-school goals and the supports, courses, and services that will help the student to attain these goals. The ITP becomes an essential component of a student's IEP; in fact, the post-school goals outlined in the ITP should drive the contents of the IEP, including annual goals and transition services [2].

IDEA [1] calls for transition planning to be highly individualized – based on a student's preferences, interests, strengths, and needs. To ensure individualization, students and their family members should be highly involved throughout the entire transition planning process. Additionally, schools should connect students and families with local adult service agencies that align with a student's individual needs. Transition planning should focus on improving students' academic and functional skills to facilitate the movement from school to all post-school activities [3].

From Entitlement to Eligibility-Based Services Generally speaking, most children with disabilities receive many services during the school-aged years. These services vary depending on individual needs, but may include special academic instruction, speech and language services, occupational therapy, physical therapy, adapted physical education, and/or vocational skills training. As outlined in a student's IEP, school-based services are entitlement based, meaning the student is legally entitled to receive services under federal law [1].

Once adolescents with disabilities graduate or age-out of the school system, two main changes occur. First, services are no longer provided in the school setting, nor are such services even provided in a single place. In contrast to schools, which essentially operate as one-stop service providers, during adulthood the individual with disabilities must travel to different locations in the community and coordinate different agencies' services.

Second and more importantly, services during the adult years are no longer mandated by federal law. Instead, they are eligibility-based, with each agency or service provider having unique eligibility criteria. These services are provided through state-funded agencies *at the discretion of the state*. In most states, the need for services outstrips the supply, and across the United States, *only about ¼ of all eligible individuals with IDD currently receive adult disability services* [4]. As a result, many adults with disabilities are placed on waiting lists for years – sometimes only to be told they are not eligible to receive the service.

For young adults and parents alike, these changes in the structure and scope of services can feel overwhelming. Indeed, many have shared

their difficulties in attempting to "navigate" the world of adult services [5]. To prevent a disruption in disability services, transition planning should incorporate interagency collaboration, wherein students and their families are connected with potential adult service providers prior to leaving the school system. Student and family involvement in the transition process is critical; those who are in contact with service providers are certainly more likely to obtain services than those who are not.

Student and Family Involvement Simply stated, the most important members of the transition planning team are students and their parents. To ensure a successful transition, the team must develop a meaningful transition plan that (a) incorporates the student's preferences, interests, and strengths and (b) will be carried out by the student and their family after they leave school. For these reasons, adolescents with disabilities and their family members must play a large role in the planning process, all the way from discussing post-school hopes, to identifying meaningful supports that fit with their lifestyle, to participating in transition planning meetings at the student's school.

Although IDEA largely avoids discussing student participation during IEP meetings for younger children, this changes once a child reaches transition age. When transition planning will be discussed at an IEP meeting or the student is aged 16 years or older, IDEA requires that the student must be invited to attend the meeting. In fact, IDEA mandates that transition planning, and the corresponding transition services and activities that arise from such planning, should be based on the student's individual preferences, interests, and needs. Schools are tasked with conducting transition assessments to provide insight into a student's strengths, including potential future careers. In recent years, increasing numbers of adolescents are attending their own IEP meetings [6], with specific interventions now designed to help them participate [7]. If students share their post-school desires, the transition planning team can use this input, in combination with assessment results and family contributions, to create a meaningful plan that aligns with student interests.

It is also important to emphasize the role played by the family, especially parents (usually, mothers). Throughout this process, parents play both informal and formal roles, often serving as the "linchpin" in coordinating services [8]. Informally, parents may spend time talking to and counseling their young adult with disabilities, offering advice and guidance as their child prepares for the changes and challenges associated with young adulthood. More formally, the parent is a mandatory member of the transition planning team, collaborating with teachers and other school officials. Given the complexity of dealing with separate adult agencies that oversee services related to employment, Social Security Insurance (SSI), Social Security Disability Insurance (SSDI), postsecondary education, health, and other services, recent initiatives are training parents how to effectively navigate the many adult service agencies [9].

Furthermore, parents should actively participate in transition planning meetings, offering their input and preferences in regard to their child's post-school future. Unless parents obtain guardianship or conservatorship rights, however, the individual with disabilities holds the ultimate say as to what services will be provided and in which ways. Ultimately, by being involved in the transition process and knowledgeable about available adult services, parents and families become better prepared to help their adolescent overcome challenges associated with this transition.

Challenges Faced by Transition-Aged Youth with Disabilities Although many adolescents struggle to build and maintain friendships, navigate sexuality, and make decisions about their adult lives, this period can be particularly difficult for students with disabilities. In contrast to typically developing adolescents, most adolescents with developmental disabilities have delayed cognitive and/or social skills. To meaningfully participate in their communities, adoles-

cents and young adults with disabilities must continue to develop daily living, adaptive, and social skills. Further, some individuals with disabilities engage in problematic behaviors. Unmanaged behavioral issues can interfere with individuals' ability to secure and maintain employment, develop meaningful relationships, and live on their own.

To support students with disabilities, special education takes a long-term approach to prepare for transition. In certain respects, children without disabilities have long been preparing for transition. Even young children informally contemplate their adulthood when they talk endlessly about their ever-changing plans for the future (e.g., "I want to be a firefighter/doctor/policeman when I grow up"). More formally, school-age children begin preparing for adulthood when they talk to their parents about potential careers or discuss career planning with their guidance counselors. Students may take specific classes or perform extracurricular activities needed to get into colleges with programs in their desired fields.

On the other hand, children with developmental disabilities may often experience a different transition process. It is probably less common that a child with a developmental disability is asked what they want to be when they grow up. Additionally, some youth with disabilities lead sheltered lives, with little opportunities for unsupervised experiences or decision-making [10]. As such, some adolescents may be uncertain of their preferences and/or dislikes, including what type of jobs, education, or living experiences they may prefer in the future. Moreover, informal and formal preparations for transition may also differ, as the child's independent functioning as an adult gradually becomes *the* important issue for the adolescent with a disability and his or her family.

Unfortunately, in many instances, transition planning for youth with developmental disabilities focuses on deficits and required supports, possibly limiting the individual's post-school options. Instead, the IEP team should employ a strengths-based approach, wherein a post-school plan is built upon the adolescent's strengths, hopes, and dreams. By employing this more hopeful perspective, the team can consider a wider range of options, including postsecondary education programs and/or certain career paths.

A further difference involves the lengthening life spans of persons with disabilities, particularly among those with genetic syndromes. As recently as a few decades ago, most individuals with Prader-Willi syndrome did not commonly live past their middle-aged years. With increased attention to weight management and the prevention of obesity, more and more people with this syndrome are now living longer lives [11]. Indeed, if a "person with PWS can control both obesity and other complications of the condition, they can expect few, if any, changes to their life expectancy" [12]. As a result, the needs of individuals with disabilities and their families have changed. The lasting impacts of decisions made as the individual transitions from adolescence to adulthood must be considered. Though many youth will undoubtedly face challenges in their journey to adulthood, certain practices – such as person-centered planning – can facilitate the transition process for adolescents with disabilities.

Person-Centered Planning Person-centered planning (PCP) is a planning practice that helps individuals with disabilities and their families to identify meaningful outcomes based on the strengths and desires of individuals with disabilities [13, 14]. Rather than determining goals based on existing supports and services, PCP focuses on possibilities and creating robust networks to support the persons with disabilities to meet their daily needs and achieve their postsecondary goals [15].

While there are a variety of approaches to PCP, most techniques share certain commonalities. Most approaches begin by gathering a team of people who know the person with disabilities well. This team typically includes parents, siblings, family members, friends, peers, neighbors, service providers, teachers, and, most importantly, the individual with disabili-

ties. A facilitator is often used to guide discussions and record ideas.

The team convenes to discuss the individual with disabilities and plan for their future. Using a strengths-based approach, team members work to set goals and "identify opportunities for the individual to develop personal relationships, participate in their community, increase control over their own lives, and develop the skills and abilities needed to achieve these goals." Team members pledge to complete specific actions to ensure that the strategies discussed in meetings are implemented. For example, a family friend might commit to helping the individual secure an internship at a local business, while an uncle may volunteer to provide transportation to and from medical appointments. The team reconvenes periodically to check on progress and find new ways to meaningfully support the individual with disabilities. Common PCP approaches include Circles of Support [16], Making Action Plans (MAPS) [14], Personal Futures Planning (PFP) [17], and Planning Alternative Tomorrows with Hope (PATH) [18].

Though PCP can occur at any point during a person's life, several PCP components align with transition planning. These include involving those with whom the individual has a close relationship, identifying ways to support community participation and inclusion, relationship-building, and using natural supports when possible [19]. At the core, transition planning and PCP share similar goals: To prepare individuals with disabilities for postsecondary employment, education, independent living, and community inclusion [15]. With a focus on self-determination, PCP can emphasize the desires of the student and family during this critical planning period.

PCP meetings generally occur outside of school; however, to create a more comprehensive Individualized Transition Plan, students with disabilities and their families can share the outcomes PCP during transition planning meetings. By involving family members, friends, and others, all of those who are closest to the student come to appreciate their roles as support providers and advocates, as well identify strategies to facilitate community inclusion.

Transition Domains

Given the larger issues that contextualize transition, we now turn to the main areas in which transition occurs.

Employment Postsecondary employment is among the most important goals of the special education transition process [20]. Long before the first day on the job, employment is something that an adolescent with a disability must prepare for. In most cases, schools teach vocational skills to students with disabilities during the transition period. In high school, a student may be taught interviewing skills, how to fill out an application, and how to use public transportation. Some students with more extensive support needs may be given opportunities to volunteer at community businesses or organizations for a few hours each week.

Although schools usually do not directly help with job placements, certain adult services do aid in this process (e.g., the state's Department of Vocational Rehabilitation). The person with the disability, with their family, can meet with such agencies and request their participation in the transition meetings. Connecting with these agencies as early as possible, while the student is still in high school, is critical to avoid long wait lists and/or a disruption in needed services.

With support from their families and/or service providers, individuals with disabilities may consider various types of paid vocational positions (see Table 14.1). At the least restrictive end of the continuum is competitive integrated employment, or "typical" jobs working alongside nondisabled persons in the community and earning competitive wages. In the middle are options such as customized employment and supported employment, which offer the individual with a disability an opportunity to work in a community setting, alongside nondisabled peers, but with supports necessary to be successful. In the most restrictive vocational settings, positions provide more specialized supports, but are segregated from the community and nondisabled workers. In addition, any one job placement should not necessarily be thought of as permanent position. A

person may move across levels of support, as needed, at different points in time.

Education/Training While many people assume that postsecondary education (PSE) solely refers to college or university coursework, PSE is actually a broad term that refers to any educational experience after high school. Postsecondary education options can include anything from adult transition programs, to vocational training programs, military service, or working toward a degree at a college or university. Most young adults with disabilities do plan to attend some sort of PSE program. Like employment and residential settings, determining a PSE setting will depend on an individual's interests and post-school goals.

In the past decade, increasing numbers of colleges and universities across the United States have developed PSE programs for individuals with an intellectual disability (ID). Over 300 such programs currently exist, for example, Think College [21]. These college programs are inclusive, with students attending classes on the college campus and, in some cases, even living in dorms. The programs are, however, specifically designed to meet the needs of students with ID, offering modified coursework, peer supports, vocational training and internships, functional skills workshops, and personalized advising. Students who complete such a program earn a certificate, usually in vocational studies, thereby enhancing their employment opportunities. In contrast to the typical college admissions process, students attending these programs are not required to have obtained a high school diploma or to submit SAT or ACT scores. Rather, students must share documentation of their disability,

Table 14.1 Paid work opportunities from least support to most support needed

Term	Description	Examples	
Competitive integrated employment	A job like that of nondisabled persons, with the same pay levels and benefits. This also means that the person is expected to have the same job responsibilities and performance as other employees	Cashier, stock person, utility clerk, landscaping crew, factory employee	Least restrictive
Supported employment	Same sites as a person with competitive employment but with more support services, offered through rehabilitation service agency. Generally, a job coach, or someone specifically trained to offer job support to persons with disabilities, will teach persons the basic skills needed to maintain their jobs	Same as above but with support	
Customized employment (CE)	Same sites as a person with competitive employment but with support services and negotiated job responsibilities. In CE, an individual's strengths and skills are matched with employers unmet business needs	Customized duties, based on strengths and interests and business' needs	
Sheltered work	Individuals with disabilities are in a more restricted setting, in a segregated environment, and they work in groups with other individuals with disabilities	Packaging and/or product assembly of office supplies, jewelry, etc.	Most restrictive

apply to the program, and demonstrate readiness and enthusiasm for attending college.

Independent Living For any person, moving out of their family home is a major milestone. This decision affects the family, as well as the person, and this may be even more true for persons with disabilities. The appropriate time to move out of the family home differs for each person, and compared to those in the general population, most individuals with disabilities leave their family home at later ages [22, 23]. The decision is affected by such factors as the young adult's readiness – including their willingness and functional skill development – to move out and parental attitudes toward moving out, both of which can also be affected by such factors as culture and socioeconomic status. To make informed decisions, one needs to know about the various residential placements available for persons with disabilities.

Just as in school or in employment, residential opportunities vary from least to most restrictive, with "most restrictive" signifying placements that generally offer the most support and are most segregated from the community. Considering residential placements on a continuum from least to most restrictive, a person with a disability may live independently or with some support in a semi-independent living situation (in their own house or apartment), in a large or a small group home (sometimes called community care facilities), in an intermediate care facility, or in a state developmental center or a state hospital (see Table 14.2).

Of special interest here is one type of group home, specialized Prader-Willi group homes [24]. These placements are group homes – with

Table 14.2 Living options from least to most restrictive environments

Residential setting	Description	
Independent living	The individual with the disability may choose to live alone in a home that they own or lease in the community. They may have hired staff that aid in some daily activities, but do not require supervised care and training in basic life skills	Least restrictive  Most restrictive
Supported living	The individual with the disability has support systems, typically trained nondisabled roommates or outside agencies that teach independent living skills. In most situations the person is monitored and supervised because they may not yet have mastered basic life skills. They learn to manage these duties while living either alone or with roommates in an apartment or condominium	
Group homes or community care facilities (CCF)	Offer 24-h nonmedical residential care to individuals with developmental disabilities who may need personal services, supervision, and or assistance crucial for self-protection or sustaining the activities of daily living. These residential models are popular because of their integration into the community	
Intermediate care facilities (ICF)	Offer 24-h service to 4 to 16 individuals with disabilities. These facilities serve individuals with developmental disabilities who have a primary need for developmental services, as well as some needs for skilled nursing services	
State hospitals or developmental centers	Serve individuals who need 24-h supervision in a structured health facility where they receive programming, training, care, and treatment on-site	

six to eight individuals living in a home within a residential neighborhood – in which all residents have Prader-Willi syndrome. In these homes, services are tailored to meet the needs of residents, with refrigerators and food cabinets oftentimes locked. Most Prader-Willi group homes also feature exercise rooms and arrange exercise times for residents each day. Staff members are specially trained to work with individuals with this syndrome. Because of their specialized nature, these group homes are an attractive residential option for many families and adults with Prader-Willi syndrome.

Community Inclusion In transition planning, the primary domains of employment, postsecondary education, and independent living are important, but not necessarily address the need for relationships and community inclusion [25]. Community inclusion, or meaningful social involvement in events and activities within the local community, is a key indicator for quality of life for adults with disabilities [26]. In general, schools promote community inclusion by helping students obtain the life skills needed to live and participate in their communities. Such basic skills might involve taking public transportation, shopping for clothes or food within a certain budget, using the post office, attending religious services, or visiting their doctor or a health clinic. Other services might help lessen the adolescent's maladaptive behavior or teach appropriate social skills, thereby fostering meaningful participation in community programs, activities, and events.

Transition Issues Specific to Prader-Willi Syndrome

Until now, we have discussed transition with only slight mention of Prader-Willi syndrome. Our reasoning has been that, regardless of the individual's type of intellectual disability, similar or identical issues arise. Adults with any intellectual or developmental disability must learn how to meaningfully participate in their community and how to engage adult service personnel to make such life decisions as where to work or live. These common issues also include difficulties that individuals and their families experience in navigating more fragmented adult service systems. Further, in many states in the United States, the demand for services often exceeds what state systems or other agencies can actually provide, leading to long waiting lists for services [4]. Complicating these many common challenges are the specific needs of transitioning youth with Prader-Willi syndrome.

PWS Behavioral Issues Affecting Transition As Prader-Willi syndrome is a relatively rare disorder, adult service providers may not routinely encounter young adults with the syndrome. Indeed, these workers may initially be stymied by individuals with PWS because they present with strengths and challenges that don't neatly fit into their usual practices. Many young adults with Prader-Willi Syndrome have relatively well-developed cognitive and verbal skills, suggesting that they are good candidates for living independently or being competitively employed with minimal supports. And while some individuals can do so, most adults with Prader-Willi Syndrome require more intensive levels of care or supervision that is not predicted by their IQ alone.

Young adults with Prader-Willi syndrome often show less-than-optimal everyday adaptive performance due to a wide array of syndrome-related behavioral characteristics. Such characteristics include hyperphagia and heightened risks of obesity; mild to moderate intellectual disabilities; social cognitive deficits; compulsivity, rigidity, and insistence on sameness; anxiety; and temper outbursts [27–30]. For youth that are transitioning to community-based, vocational, or residential placements, four behavioral characteristics are especially important.

1. Hyperphagia Hyperphagia onsets in childhood and is associated with dysfunctional neural networks involved in both satiety and reward. The impaired satiety response results in a state in which individuals are habitually hungry yet rarely feel full [31]. Holland, Whittington, and Hinton have aptly described Prader-Willi syn-

drome as a state of starvation that manifests as obesity in food-rich environments [32]. While the severity of hyperphagia varies across individuals and over time, people with Prader-Willi syndrome often engage in food-seeking behaviors, sometimes in very clever ways. They may sneak food, manipulate others or bargain for food, and repeatedly ask about meals and food [33]. People with Prader-Willi syndrome are thus at high risk for obesity and require such external controls as vigilant supervision around food; locking food sources (e.g., kitchen cabinets, pantries, refrigerators); a reduced calorie diet; providing meals at predictable times; and ensuring food security in school, work, and community settings [33]. Supervision around food may need to increase in new environments and during transitions or stressful times [34].

Further, hyperphagia is life-threatening; [11] found that most deaths in Prader-Willi syndrome relate to complications of obesity (e.g., type 2 diabetes, respiratory and circulatory problems). Other food-related causes of death include choking while rapidly consuming food and acute gastrointestinal distention, perforation, and necrosis, typically after relatively slender but formally obese individuals engage in binge eating. Clinical trials testing the efficacy of agents in curbing hyperphagia and related symptoms have been completed; others are currently underway or planned for the future [35–37]. Although some are promising, none have yet been approved by the FDA and, as such, are not readily available for treating individuals with Prader-Willi syndrome.

Transitioning out of high school presents a set of conflicting expectations for managing hyperphagia in Prader-Willi syndrome. On the one hand, these youth are striving for more independence and solidifying their goals for future employment, education, job training, and recreational opportunities. In doing so, person-centered planning places the individual with intellectual disabilities in the driver's seat in terms of making such life decisions.

To avoid such complications of hyperphagia as obesity, poor health, or premature death, however, these individuals still need intensive supervision around food. The challenge for transition and adult service workers, then, is how to optimize independence and a successful transition into adulthood while also ensuring food security and good health. Living, working, and recreating in the community are goals for many individuals with intellectual disabilities. Yet community-based activities for those with Prader-Willi syndrome are complicated by the fact that food is so readily available. As succinctly stated by two young adult participants in an interview study [29], "PWS affects the way things go in the community because you can't go where they have food around." And "Fast food, it's everywhere. I am surrounded by food that I shouldn't eat. Am struggling very hard."

Clearly, a balance must be reached between the meeting needs for food security and supervision of youth with Prader-Willi syndrome and placing them in programs aimed at facilitating their independence and educational and employment goals. Doing so depends on accurate knowledge of Prader-Willi syndrome combined with the creativity and best practices of transition professionals.

2. Maladaptive Behaviors Relative to others with intellectual disabilities, people with PWS more often exhibit aggression, irritability, compulsivity, insistence on sameness, and rigid thinking [29]. Typically, these individuals become upset at sudden or unexpected changes in their schedules and are prone to such compulsive behaviors as skin-picking, repetitive questioning, ordering and rearranging items, and hoarding of non-food items [28]. For example, many young adults with Prader-Willi syndrome become "stuck" and need particular help during transitions. Such difficulties in dealing with breaks in routine or other unexpected events also result in many individuals with Prader-Willi having full-blown, disruptive temper outbursts. Such outbursts can arise around food-related or other issues; they also often occur when the individual's routine has been disrupted. Temper outbursts are especially problematic when they occur during work, in a group home, or out in the community.

Two additional issues also deserve mention as they have direct bearings on transition-aged youth. First, behavior problems may wax and wane over the life course. Although present for many individuals from early childhood years on, behavior problems may also prove especially problematic during the transition years. Cross-sectionally examining a large sample of 3- to 50-year-olds, Dykens [38] found that maladaptive behaviors generally increased throughout childhood up until about age 30, after which problems decreased from age 30 to 50. This "up until 30, then down" pattern held for the overall amount of behavior problems, the amount of problems directed toward others (e.g., such externalizing problems as tantrums or aggression), as well as for skin-picking and for the individual's number and severity of compulsive symptoms.

Second, specific, severe maladaptive behavior has been tied to one particular type of Prader-Willi syndrome, maternal uniparental disomy, or mUPD. Occurring in about 1/3 of all individuals with Prader-Willi syndrome, individuals with mUPD receive two copies of chromosome 15 from the mother. These individuals show high levels of such psychotic symptoms as delusions and hallucinations, sometimes occurring with depression or other mood disorders [39]. These psychotic symptoms, which occur in from 75% to 100% of adults with mUPD, first appear sometime during the transition years. In Boer et al.'s original study, psychotic symptoms first occurred at an average age of 28.5 year. In a subsequent report, Sinnema et al. [40] found mean onset ages during the early 20s, with those with psychotic symptoms alone having a mean onset age of 20.5 years and those with psychotic symptoms and depressive disorder an onset age of 21.8 years. With or without co-occurring affective symptoms, psychotic symptoms among those with mUPD often first occur during the transition from school into adult life.

3. Social Difficulties Partially related to both hyperphagia and other maladaptive behaviors, individuals with Prader-Willi syndrome often display difficulties getting along with others, relating to peers, and maintaining friendships. Many individuals with Prader-Willi syndrome also show impairments in accurately perceiving the emotions and intentions of others. In a large-scale, longitudinal study of this issue, three groups of individuals with Prader-Willi syndrome were examined, ages 5–10 years ($N = 44$), 11–19 ($N = 34$), and adults 20 and over ($N = 16$; Dykens et al. [29]. Over the 2 years between tests, individuals improved in recognizing most emotions (in response to standardized photos), even as they often confused sadness and anger. More importantly, however, these individuals misinterpreted social perceptions, the process of using social information to infer another's intentions. In all three groups and over the two tests, most participants had difficulty differentiating between when a character in a vignette had made an honest mistake as compared to when that character was being insincere, hostile, teasing, lying, or rejecting. Consider, for example, a vignette in which one character inadvertently bumps into another, causing papers to drop and scatter across the floor. In response to that vignette, most respondents did not take advantage of a clear, blatant cue – when the character said: "I'm so sorry. I should have been watching where I was going" – in order to draw the correct conclusion that the story character was "not being mean." As a result, young adults may misinterpret benign social mishaps (accidently bumping into someone) as people being "mean," more often attributing hostile intent to benign behaviors. This type of negative social bias would seem detrimental in forming friendships during the early adult years.

4. Interests, Strengths, and Propensities People with Prader-Willi syndrome also often display propensities toward specific activities that might be considered in the transition process. More than others with disabilities, both men and women with Prader-Willi syndrome seem drawn to taking care of pets or children [41]. Although not well-studied, this desire to caretake may be associated with aberrant plasma or CSF levels of oxytocin [42], a neuropeptide associated with human bonding and other functions. A propensity toward nurturant behaviors may inform work or leisure choices during adulthood. Many indi-

viduals aspire to work or volunteer taking care of animals in pet stores or as veterinarian assistants. Still others want to work in day care or other child-oriented settings.

Similarly, many individuals with Prader-Willi syndrome gravitate to word-find and jigsaw puzzles. Many perform these puzzles quite proficiently, on par or exceeding chronological age- matched controls [43, 44]. Recreational use of electronic or computer games may confer some cognitive advantage to adults, even as increased computer or TV screen time has also been associated with higher BMIs in adults with Prader-Willi syndrome [45]. More work is needed to understand how such interests might relate to work, leisure, or residential activities during early adulthood. Alternatively, such activities may be an important source of gratification and feelings of self-efficacy.

PWS Residential Issues

Many parents and professionals feel that most adults with this disorder benefit greatly from specialized Prader-Willi group homes [24]. These placements are group homes – with six to eight individuals living in a home within a residential neighborhood – in which all residents have Prader-Willi syndrome. In these homes, services are tailored to meet the needs of residents, with refrigerators and food cabinets oftentimes locked. Most Prader-Willi group homes also feature exercise rooms and arrange exercise times for residents each day. Staff members are specially trained to work with individuals with this syndrome.

Although the focus of only a few studies, Prader-Willi group homes, because of their specialized nature, do appear to benefit most residents with this syndrome. Adults residing in these group homes have lower BMIs (body mass index, a measure of weight and obesity) [38] and lower rates of maladaptive behavior [46]. However, more segregated, specialized residential settings generally go against the current emphasis on inclusive programming. An overemphasis on inclusive programming may also negate the need for programming that relates to each individual. Specifically, while many young adults with the syndrome can handle unsupervised coffee breaks at work or helping to plan the group home menu, others may not. In addition, food supervision may need to increase in new environments and during transitions or stressful times, before returning to baseline later [34]. Clearly, a balance must be reached between the needs of the young adult with Prader-Willi syndrome and the idea that all persons with disabilities live as typically and as normally as possible.

PWS Physiological Issues Affecting Transition

In addition to behavioral characteristics, most adolescents and young adults with Prader-Willi syndrome also face physiological issues that may impact their successful transition to adulthood. In particular, individuals with Prader-Willi syndrome are affected by hypogonadism, or failure of the sex organs to develop and function properly. For many individuals with Prader-Willi syndrome, hypogonadism causes issues with puberty. In some children, premature development of pubic hair can occur as early as 8 years old. However, this premature hair growth does not align with the onset of puberty, which may actually be delayed. When puberty does occur, male sex organs rarely reach full development, and females face sporadic, delayed, or no menstruation [47]. Additionally, many individuals with Prader-Willi syndrome who experience hypogonadism also experience infertility. In recent years, hormone therapy has been studied as a promising way to treat symptoms associated with hypogonadism [48].

Though they may experience physiological sexual issues, many individuals with Prader-Willi syndrome do have a normal sex drive and are interested in romantic and sexual relationships [49]. This desire for sexual intimacy may become apparent during the transition years, as individuals with PWS see their peers developing intimate relationships. However, compared to their typically developing peers, persons with PWS may

be at risk for sexual exploitation and abuse due to increased naiveté (e.g., trusting strangers) and vulnerability [50]. Families will need to consider a variety of factors as they navigate issues of sexuality and "what is best" for the individual with PWS.

Recommendations

Though over the years our knowledge of Prader-Willi syndrome has grown, we need to better understand how the syndrome impacts the transition to adulthood. Throughout this final section, we offer recommendations intended to improve outcomes in the following areas: transition services, adult services, addressing problematic behavior, family involvement, and future research.

Transition Services IDEA calls for transition planning to formally begin by the time the student turns 16 years old. However, we recommend starting this process as early as possible. We encourage parents, educators, and service providers to begin the conversation, even informally, at a young age. By using a person-centered planning approach during transition planning, the young adult with Prader-Willi Syndrome and other key people can voice their preferences and desired future outcomes. Asking the individual and their family what they want can help them set goals and form a realistic plan for their future.

As a step toward achieving post-school goals, we also recommend that, during their high school years, adolescents with Prader-Willi syndrome participate in a curriculum that emphasizes both functional skills and vocational training. Functional skills range from eating, toileting, and self-hygiene to functional academic skills (e.g., reading, writing, basic math, etc.), whereas vocational training helps in acquiring such employment-related skills as career awareness and exploration, interviewing skills, problem-solving, and even work experience. By helping youth with Prader-Willi syndrome acquire functional and vocational skills before adulthood, we can prepare them for better post-school outcomes and more independent adult lives [51].

Adult Services The change from school-based services to adult services can be difficult to navigate for many families. One way to ease this transition is through interagency collaboration. By including potential adult service providers in transition planning meetings, service providers can outline services and eligibility requirements and answer questions students and families may have. By connecting families with adult service providers early in the transition process, young adults with Prader-Willi Syndrome and their families can become aware of potential service agencies and, in some cases, join waitlists to reduce the chance of disruption of needed services between school and adulthood.

Difficulties will also be alleviated by educating adult service providers about Prader-Willi syndrome. Even compared to parents of children with such conditions as Down syndrome or autism, parents of young adults with Prader-Willi syndrome may need to educate professionals [52]. Parents should be forewarned that few adult service staff – be they case managers, vocational rehabilitation counselors, job coaches, or (generic) group home staff – will have heard about the syndrome. Fewer still will truly appreciate the difficult management issues presented by young adults with Prader-Willi syndrome. Providers need to understand the physiological basis of overeating – it is not willfulness or poor self-control. Training service providers how to work with adults with Prader-Willi syndrome and implement effective interventions can lead to a smoother transition to adult services, a higher quality of life for individuals with the syndrome, and peace of mind for family members.

Addressing Hyperphagia and Social Skills Deficits In addressing behavioral issues in Prader-Willi syndrome, a major issue relates to food. As the severity of hyperphagia varies across individuals, there is no one-size-fits-all answer to this dilemma. One person, for example, may handle unsupervised coffee breaks at work; another may use it to sneak food. It is critically important that educators, vocational counselors, and adult service providers appreciate that hyperphagia in Prader-Willi Syndrome is

not a matter of willpower or self-control. Instead, it is a lifelong condition associated with aberrant neural functioning. As such, one obvious rule of thumb for service providers is that they should try to obtain job placements outside of the food service sector.

In addition to these larger issues, several techniques have proven helpful. In terms of food management, techniques include vigilant supervision around food, locking food sources (e.g., kitchen cabinets, pantries, refrigerators), a reduced calorie diet, and providing meals at predictable times [33]. Recent years have also brought forth the concept of "food security," the idea that – across such diverse settings as school, work, home, and community – parents and caregivers lock food and supervise the appropriate intake of food by the person with Prader-Willi syndrome. A multi-pronged approach, followed by all parents, other family members, and service personnel, all seems necessary.

An additional behavioral support concerns using special interests and propensities for work or leisure. Many adults with the syndrome show passionate interests in nurturing animals – working in pet stores or animal rescue centers might prove a useful fit between the adult's interests and a meaningful job or activity. So too might interests in jigsaw or word puzzles be tweaked to aid in leisure or job endeavors. Although few studies are yet available to document such person-job connections, each would seem at least potentially useful in everyday activities that might aid these adults in becoming integrated into wider community settings.

So too might specific interventions help young adults with Prader-Willi syndrome improve in their social skills. Recently, a distance-based social skills training program was provided using the Building Our Social Skills (BOSS) curriculum. Featuring an intensive, 10-week group intervention aimed at improving social skills, perceptions, and thinking, online sessions occurred 3–5 times per week, using secure technology with four to six young adults with PWS per group. All groups were led by one to two facilitators (both research staff and Special Ed graduate students) in an online setting. Regular practice of skills was built into the intervention, with fun, motivating exercises conducted at home, in the community, and with the facilitators. Preliminary findings indicate that participants enjoyed the BOSS interventions and learned several important social skills (e.g., turn-taking and perspective-taking), with friendships developed within the BOSS program sometimes continuing after the intervention period [53]. Although much more work is needed in this area, social skills training – and training that might be especially tailored to young adults with Prader-Willi Syndrome – does seem promising.

Sex Education To address issues related to vulnerability and sexual abuse, we also recommend adolescents and/or adults with Prader-Willi Syndrome participate in sex education. A proactive approach is necessary, given that many adolescents and adults with Prader-Willi Syndrome share their wishes for romantic partners and/or sexual intimacy. Sex education programs have been specially developed for individuals with ID. These programs typically cover a variety of topics that may be beneficial for persons with Prader-Willi Syndrome, including friendships, romantic relationships, social skills (e.g., appropriate vs. inappropriate behavior), and safe sex practices [54].

Family Involvement As noted, the transition process can be complicated and difficult to manage for adolescents and young adults with disabilities. We recommend that family members be highly involved in the transition planning process. Family members "should be an integral part of the IEP team contributing to decisions regarding annual IEP goals, services, and supports a student receives to prepare for the transition to adulthood" [55]. Parents need to be young adult's best advocate. Indeed, family involvement has been associated with improved in-school outcomes (e.g., academic achievement) and post-school outcomes (e.g., employment) [56]. Further, family involvement in transition planning can ensure the development of a meaningful transition plan that reflects both the student and family's preferences and values [57].

Beyond involvement in transition planning, family members are often tasked with providing lifelong supports to their kin with disabilities. Parents, in particular, provide a plethora of supports to their offspring into and through adulthood [58]. This ongoing, high-level care can be taxing, particularly for parents of individuals with Prader-Willi syndrome [59]. Parent support groups can introduce those with shared experiences and offer a way to exchange advice and resources and/or socialize and make friends.

Future Research Finally, research surrounding Prader-Willi syndrome has undoubtedly grown in recent years. However, much of the research has a medical focus; there is still a dearth of research addressing individuals with Prader-Willi syndrome from an educational or social science perspective. To address this gap, we call for an increase in research that examines the experiences of individuals with Prader-Willi syndrome and their family members as they navigate various life stages. Specifically, future research in the area of postsecondary transition planning is necessary to determine appropriate supports that best meet the unique needs of young adults with Prader-Willi syndrome and their families.

Conclusion

The transition from school to adulthood can be difficult for any adolescent, as they and their families make critical decisions surrounding adulthood. For youth with Prader-Willi syndrome, the transition process can be even more taxing as they encounter unique challenges related to their disability, including managing problematic behaviors and securing appropriate adult services. And yet, as overwhelming as these challenges may seem, individuals with Prader-Willi syndrome and their families can survive – and even thrive – throughout this process. We encourage parents of adolescents with Prader-Willi syndrome to learn as much about the transition process as they can – participating in transition planning meetings at school, linking with adult service providers early on, and connecting with other families of young adults with Prader-Willi syndrome who have gone through this process. Being knowledgeable about the transition process and the various supports and services available makes it possible for the young adult with Prader-Willi syndrome to lead a high-quality and independent-as-possible adult life.

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Vocational Challenges for People With Prader-Willi Syndrome

15

Steve Drago

The Last Hurdle

The standard of care for persons with Prader-Willi syndrome (PWS) continues to evolve rapidly and dramatically. People with PWS now are routinely diagnosed at an early age, the majority in the newborn period. Physicians are better educated about the disorder, and effective treatment protocols are continuously emerging. Hormone therapies are resulting in people who are healthier and more energetic and robust and who look "normal." Many children with PWS are successfully mainstreamed in school. Effective behavioral management strategies have been developed and are readily available. In contrast to several decades ago, today residential placements exist that effectively manage the behavioral and weight issues of people with the disorder.

Because of these improvements in health care, education, and behavior management, more and more individuals with PWS are living well into adulthood, often into the fourth and fifth decades of life. As a result of the rapid improvements in both the length and quality of life, the bar of parental expectations has been raised. Parents are no longer merely concerned that their affected child *will survive*; rather parents want – and expect – to see their son or daughter *thrive*, live a normal life, and be included in the fabric of their communities. More importantly, the aspirations of people with PWS have changed as well. Many now expect to eventually live independently, in their own home, perhaps with a spouse and pets (not necessarily in that order), and to be gainfully employed. Expectations for good health and for satisfying adult living situations are no longer unrealistic. In the continuum of effective services for people with PWS, successful job placements have evolved to the status of "the last hurdle" to be cleared.

Effective vocational placements are still difficult to achieve for people with PWS, despite extensive health and adult care improvements. There are several reasons why this is so. First, vocational providers have not had to live with the disorder; many are slow to understand the seriousness of the appetite and emotional volatility associated with the disorder. The truly debilitating nature of PWS is often difficult to grasp until time is spent working or living with an affected individual. One parent uses the analogy of alcoholism or drug addiction to describe her son's disability: "His drive to eat is just as strong and difficult to overcome as any other addiction." Unlike someone addicted to drugs or alcohol, however, her son cannot simply stop imbibing or using. He *must eat*; furthermore, he *must eat several times per day*, in small, controlled quantities,

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and *then stop*. Unlike the alcoholic or drug addict, an individual with PWS is unable to simply adopt a new lifestyle by surrounding himself with people who do not use alcohol or drugs or by avoiding places where these things are used. Everyone eats, and food is everywhere in our society. Thus, the stress on an affected individual is ubiquitous and constant. Until and unless an employer achieves this level of understanding and appreciation of the disorder, job placements have a higher likelihood of failure.

Even for the most willing to learn, an employer's effort to fully understand the challenges of serving someone with PWS is often undermined by first impressions from an introductory meeting. Usually, prospective employers are initially presented with a mild-mannered, intelligent individual who is motivated to work. Many employers have employed other people with disabilities whose initial presentation did not signify either the capabilities or the (apparent) social and intellectual skills initially observed in a person with PWS. Therefore, when the person with PWS disappears from the work site to obtain food or becomes argumentative with the boss, employers inexperienced with PWS are most likely to see these behaviors as "merely discipline problems" rather than as a natural manifestation of PWS requiring workplace adaptation.

Second, politics continues to play a contributory role in the vocational challenges. Employers who provide treatment and training in congregate settings are currently challenged with new regulatory requirements accompanied by mandates for substantially increased documentation of compliance. Previous federal wage and hour regulations that have allowed individuals in sheltered or supported employment settings to be paid less than minimum wage are now being challenged, and the escalating regulatory requirements for maintenance of sub-minimum wage certificates (14c) coupled with the costs of meeting ever-changing workplace safety requirements has forced numerous providers to discontinue onsite work and other vocational training. Many of these providers now offer only social recreational programs and supported employment in community-based settings. We will discuss these changes in greater detail later.

Third, an employer's expectations for individuals in an adult work setting are different from those at home or in school. Schooling is an entitlement; as such, schools *must* adapt for the individual. By contrast, jobs are *earned*; the employee serves by the privilege of the employer. Arguing and noncompliance, both frequent typical behaviors for someone with PWS, are not usually tolerated. Thus, an initial adjustment period is usually required, during which both employer and employee acquire new learning and skills.

Finally, as of this writing, the COVID-19 pandemic has presented a whole new set of immediate and long-term challenges for providers of vocational services and people with Prader-Willi syndrome. The medical challenges to people with the syndrome are best left to medical professionals; it is sufficient to say that persons with PWS do not always present with typical symptoms when ill such as fever. As a result, they may be at risk for a delay in identification of illness. Arbitrary things such as subtle changes in behavior, sleeping patterns, or an increase in anxiety and restlessness can indicate illness. Any delay in diagnosing a COVID infection can be fatal. In an initial response to the COVID-19 pandemic, most vocational providers temporarily ceased providing services and transportation. Providers have been forced to rethink safety and service provision protocols with COVID-19 transmission (and realistically other contagious diseases) in mind as services have reopened. For many providers, this may have required help from numerous state agencies to redesign safety protocols for congregate services and transportation. At the same time, this temporary elimination of vocational services presented numerous behavioral challenges to people with Prader-Willi syndrome as they may have had to adjust to a disruption of routine in being unable to go to work and further adjustment challenges as they returned to work. We will discuss this in more detail as well.

The Work Placement Options

Sheltered workshops Prior to discussing successful work placement strategies for individuals with PWS, a discussion of work placement options and terminology is needed. *Sheltered workshops* are the oldest and most common type of job placement for workers with developmental disabilities. These settings offer job skills training in a *nonintegrated setting*. This means that the entire work or training force is made up of "disabled" individuals. Individuals in sheltered workshops are paid on a piece-completed rate; that is, they do not generally receive an hourly wage but are paid for each piece of completed work at a rate comparable to that paid to a nondisabled person. Typical sheltered workshop tasks include packaging and simple product assembly. In the United States, workshop placements are generally funded at the state level. However, as state funding sources become increasingly unreliable, workshops are being forced to become more creative in finding paid work.

Enclaves The middle ground employment choice for individuals is called *enclaves*. Enclaves consist of small nonintegrated groups of disabled adults who go into the community to perform service types of work [1]. Workers are paid an hourly wage. Because they can be considered trainees, they can be paid at a rate less than minimum wage. Comprehensive documentation and a sub-minimum wage 14(c) certificate are required for the providers to pay individuals less than minimum wage.

Supported employment is a community-based job placement in an integrated work setting; the other workers performing comparable jobs are nondisabled. Individuals in supported employment are paid minimum wage or above and must be comparable to that of nondisabled individuals performing the same job at that location. Individuals in supported employment receive on-site supports and on-the-job training from a job coach. Provided supports are time limited, and the individual must meet required progress benchmarks.

At one time these three vocational service options were considered a continuum with individuals starting in a workshop placement and progressing through the options [2]. This concept is now outmoded and has been retired. Individuals and their families are free to choose the option that best suits their skills and provides maximum chances for vocational success and safety.

Individuals with Prader-Willi Syndrome in the Workplace

Each of these vocational settings provides its own set of challenges for individuals with Prader-Willi syndrome. The most significant challenge of *sheltered workshops* lies in their size. Workshops are generally large congregate settings where the individual with Prader-Willi syndrome will represent an exceedingly small, if not singular, percentage of the individuals served. If there have been no other individuals with the syndrome employed at this site, then an extremely limited expertise for understanding and appropriately responding to the issues common to people with PWS syndrome can be expected. Such limited knowledge can lead to accidental reinforcement of unwanted behaviors. In addition, without significant alteration of the environment, workshops have extreme difficulty in achieving sufficient food security and food safety. This absence of food security leads to increased food stealing and seeking, difficulty between workers and the affected individual, as well as an increased probability of reactive behaviors and meltdowns when inappropriate food-related behaviors are addressed. While this is not unique to sheltered workshops, it is an issue that presents special challenges to inexperienced providers and, unfortunately, can put continued employment for the person with PWS at risk.

One example of a provider failing to meet the challenges of Prader-Willi syndrome in the sheltered workshop setting is Gary. Gary attended a large, sheltered workshop where he was the first person with Prader-Willi ever to be employed there. He quickly found a girlfriend, and, predictably, they became inseparable. Most parents and

people familiar with the syndrome can write the ending. Gary quickly began gaining weight, and his girlfriend came home daily with her appetite in high gear as she had not eaten all day. Gary had convinced her that girlfriends fed their boyfriends so each day she was giving her lunch to Gary. Rather than the workshop staff recognizing their need to provide a different kind of supervision in order to maintain Gary as a productive worker, Gary was suspended. Because of unfamiliarity and a failure to adjust, there was no positive outcome for either Gary or the staff.

Work enclaves generally encompass fewer individuals thus making supervision somewhat easier. The challenges that must be addressed generally involve the environment in which the work is occurring. A mainstay of work enclave employment is janitorial work that is frequently performed in offices, usually outside office hours. Offices and desks provide numerous spaces where people keep snacks and personal items that are tempting to individuals with PWS. It is difficult to supervise someone sufficiently in this environment and still get the necessary work completed in a timely manner. If an individual with PWS discovers and pilfers a stash of snacks, not only is that individual's job placement at risk so is the overall contract for the vocational provider as most contracts specifically disallow entering desks and taking anything that may be sitting out.

Lawn work or work in other outdoor venues, another staple for work enclaves, is less crowded with such opportunities and temptations. While outdoor venues are some of the more successful placements for people with PWS, they also present supervisory challenges for inexperienced providers.

Debbie was working on a local park cleanup job. She engaged in a violation of the park rules by attempting to break into a vending machine. She was confronted by staff, and the behaviors quickly escalated as staff was issuing consequences for her behavior. A well-meaning bystander called the police. The situation was eventually deescalated but not without considerable risks. For the person with PWS, providing consequences in a public place during an emotional outburst generally does not work out well. Professionally trained staff will deescalate a situation until a debriefing discussion can be held calmly and then will proceed with this situation opportunity for education.

Another example includes a young man with excellent work skills whose heart was set on working with a janitorial crew. After several failed work trials, a contract to clean a large warehouse belonging to the Department of Transportation seemed the perfect work placement for him. After a 10-pound weight gain in 1 week, it emerged that the young man had located the storage space housing the entire Gatorade drink supply for local road crews. It was not possible to secure this area, nor was it possible to sufficiently supervise the individual; as a result this placement failed.

Even when such placements are, on the surface, successful, the cost of that success may be too much for an individual to handle. One man requested his own removal from an interstate highway rest area crew despite excellent work performance and zero weight gain. He reported that watching people throw away bags of partially eaten fast food all day was too much for him; he was afraid that the temptation was becoming too great. He preferred working elsewhere, even if it meant returning to the workshop.

Placements in the real work world are the goal for most people. *Supported employment* is one way to achieve such a placement. The supported employment coach can provide a suitable placement and on-the-job training. Until there is a medication to modify the ever-present hyperphagia, the biggest issue with "real world jobs" is usually the unrestricted food availability nature of the placements combined with the fact that supervision will be both spotty and time limited.

Many initially successful placements deteriorate after several months due to food availability. Susan was terminated for taking exceedingly long breaks. It was later determined that the fast-food restaurants in walking distance presented too much of a temptation. She was an excellent worker, and the workplace had only the excessive breaks as a complaint and could not provide sufficient supervision to prevent such occurrences.

As the previous examples illustrate, the biggest issue with employment outside the workshop setting is the unrestricted nature of the food environment along with reduced supervision. For many in these settings, maintaining dietary restrictions must rely primarily on self-control, an ability in short supply for those with PWS.

There are many creative ways for a coach experienced in Prader-Willi syndrome to address these challenges before someone loses their job or, worse, their health. The theme running through these examples is (in)experience and limited knowledge of Prader-Willi syndrome. When the author, who has 40 years' experience providing vocational and residential supports to individuals with PWS, received his first vocational applicant from an individual who had PWS, it was the applicant's mother who provided the necessary initial training and provided the resources available for understanding the special needs of someone with PWS. That initial applicant was successful and resulted in the development of a program that has served hundreds of people over 40 years. Too often, professional providers do not spend sufficient time using the invaluable resource of family. This theme will reoccur as we continue to look at vocational options.

Structuring for Vocational Success

Just as service options have changed, the profile of people with Prader-Willi syndrome applying for employment services also has changed dramatically. No longer are typical applicants exceedingly obese with numerous health challenges. It is now much more common to see healthy weight individuals that are free from obesity-related health issues. Parents have changed as well. While parents of people with PWS have always been amazing advocates for their young adult, parents today are much more versed in, and committed to, the philosophies of community involvement and inclusion.

This chapter has consistently raised the need for finding or creating experienced providers. How do you determine whether someone has the experience required to succeed in supporting the person with Prader-Willi syndrome or is willing to learn sufficiently to understand the tools required to be successful? Structure and expectations should be consistent and clear. The provider should have at a minimum two systems for tracking and structuring both food and cash/credit. Cash can be easily converted to food. When these issues are planned for, people with Prader-Willi syndrome will benefit from the security. Further, the work setting will benefit as it is clear that the ability of the individual to focus and to maintain workplace performance is improved when these things are present.

There must be a system in place to train all staff in these procedures and tracking. This system will never replace individualized programs but once in place frees staff to address many more skills. Competency must be established in staff working with individuals with PWS. Competency does not have to be boring and repetitive; many options are available today.

Progress in the field of vocational services remains behind progress achieved in medical, behavioral, and residential supports for people with Prader-Willi syndrome. The reason for this lag is obvious: arranging these environments for success is far more difficult, as their very nature lessens the capacity for controlling critical components. In sheltered workshops there is not always consistency in the ownership/management between residential and vocational service providers. Typically, supported employment requires placing adults in someone else's business whose good intentions may be eroded by behavior that adversely affects business. Nonetheless, progress has been achieved, and that progress can be directly attributable to successfully structuring the environment through staff training, physical modifications, and programmatic procedures. The "final frontier" is upon us.

For vocational efforts to succeed, environments must be examined, assessed, and modified using an experienced eye. The authors 40 years' experience providing vocational services to persons with PWS suggests one will always be one step behind. However, that should not stop one from looking at environments with the experience available and structuring it to prevent as many problems as you can.

Positive behavioral supports can provide structure, respectful support, and a sense of fairness in the hands of a well-trained certified behavior analyst. Because of the reactive nature of those with PWS, a program with a proven commitment to positive behavior supports has a greater likelihood of success [3].

Table 15.1 provides a list of questions to assist families in finding the provider who will help the individual succeed. If possible, send the survey out prior to meeting with staff, and use their answers to guide your interview.

Table 15.1 Questions for families to ask while interviewing a potential provider of vocational services

General
1. How long has the agency/you been doing business?
2. How would you describe the reputation of the agency/yourself?
3. Describe the depth of your practical experience supporting people with PWS.
4. Have you ever discharged a person from your services? How many? Did they have PWS?
5. Can you provide reference for people served who would allow being contacted?
6. Do you have written materials about your services that we could take with us?
7. Are you surveyed or accredited, and can I see a copy of your most recent licensing survey (if applicable)?
8. Give me an example of a time that you were under intense pressure. How did you handle it?
9. We all make mistakes. Tell me about a time you wish you had handled a situation differently.
Staffing hiring and training
10. Tell me how you hire and eventually select staff.
11. How do you train staff to work with Prader-Willi syndrome?
12. Describe an event where your training was demonstrated with a person with PWS.
13. Describe an event where your training was not sufficient. What did you do?
14. Tell me what you do to retain staff.
Policies and programs
15. Give me an example of how you have adjusted your policies to keep employees and clients safe.
16. Do you have a policy on communication with families? Visitation?
17. Do you have a policy regarding communication with outside providers, contractors, and medical personnel?
18. Give me an example of a program you designed for people with PWS that did not work. How did you modify it?
19. Do you create specialized programs for people with PWS? How do you address food, money, and behavioral challenges?
20. Do you train staff in physical control techniques?

This list of questions is not meant to be exclusive. The answers to these questions are meant to give you information as to whether this provider is a match for your family. There are many ways to answer the questions, and some will match your idea of a good provider, and others will not. Still others may give you something new to think about. When an answer demonstrates the person or the agency has not had sufficient experience with PWS, it does not necessarily mean you have to keep looking. It does mean you should anticipate being much more involved in your family member's care. You must therefore assess the person or agencies willingness to accept that help.

While most providers will indicate a belief that families are the experts when it comes to their family member, too often providers still will miss the opportunity to gather important information from the family – information to guide the development of a program that will provide success for the employee and a productive worker for the provider. Table 15.2 summarizes some questions that will hopefully help providers gather important information prior to vocational placement.

A Look Back: A Look Toward the Future – The Good, the Bad, the Demands, and the Possibilities

This chapter is being written at the end of the first year of "the pandemic." Unfortunately, the past year has clearly delayed progress in the field of vocational supports. The temporary and permanent closing of vocational programs has contributed to record high unemployment rates among people with disabilities. Only 17.9 percent of all people with disabilities were employed in 2020, and the figures are not rapidly rebounding in the early months of 2021. This is down from 19 percent in 2019 [4]. If you compare this to the general population with 61.8 percent employment, the disturbing trends evident in 2020 trends are quite apparent [5].

Table 15.2 Interview questions for providers of services to ask of prospective employees and their family

1. Tell me about your expectations of me and this vocational placement.
2. Have you attended preparatory workshops regarding the range of vocational places available for your family member?
3. Have you received guardianship for your family member, and if not do you intend to apply for such?
Background regarding the individual with Prader-Willi syndrome
4. Tell me about your family member's strengths/weaknesses.
5. How do these strengths and weaknesses affect their relationships with peers, parents, and siblings?
6. Who are the most important people in your family member's life?
7. Describe vocational opportunities and where they see their family member succeeding, failing? Do you think if I ask your family member that question they will agree?
8. Does your family member have any preoccupations or attachments to objects or people?
9. Tell me if your family member has any medical limitations. How will your individuals' medications be secured? Administered? Will staff need to administer any of the medication?
10. Does your family member have a religious affiliation? Which church or synagogue do they regularly attend? Will there be any religious holidays for which a day off from work must be granted?
11. Are there benefit limitations to the number of hours your family member can work?
Program issues
12. Many people with PWS occasionally struggle with transitions. Can you give me some examples of transitions your child struggles with and how you handle them?
13. Many people with PWS have behavioral challenges. Can you describe what your family member does when they are upset? How do you get them calm? How long does it take?
14. What is your preferred method of handling behavioral challenges? Is your method usually or occasionally successful?
15. Are you currently using a behavior specialist to assist with care?
16.Tell me your dreams and ultimate goals for your family member.
17. What assistance do you anticipate needing to ensure a smooth transition?
Agency policies and staffing
18. When we communicate with you, what is your preferred method (phone, written, text)?
19. What are your expectations of how disagreements will be resolved?
20. For what issues/incidents would you like to be contacted immediately? What is the best method to reach you?
21. What are your preferred days/times for team meetings?
22. Will you need assistance from staff with transportation?

Nonetheless, vocational services and the supports for them continue to evolve, and new challenges continue to arise. At the time of the writing of this chapter, two immediate concerns raise substantial challenges: (1) the elimination of the federal sub-minimum wage program and (2) the ongoing impact of the COVID-19 pandemic.

Let us first address the sub-minimum wage. There are differing views and arguments for either retaining or eliminating the current sub-minimum wage status for persons with "disabilities." The program, known as 14(c) exception, has been in place since 1938. National Disability groups have clearly gone on record supporting the elimination of the program, and there is evidence that the phasing out has begun, suggesting that a complete elimination of the program may be imminent.

On July 22, 2014, Congress passed the Workforce Innovation and Opportunity Act (WIOA), which amended several provisions of the Rehabilitation Act of 1973 (Rehab Act). Among those changes, WIOA added Section 511 to the Rehab Act that prohibits providers of services to people with disabilities that hold special wage certificates under 14(c) of the Fair Labor Standards Act (FLSA) from employing individuals with disabilities at sub-minimum wage unless certain conditions are met. Ultimately, Section 511 does not change the purpose of the Rehabilitation Act, promote sub-minimum wage employment, eliminate sheltered workshops, or eliminate sub-minimum wages. Rather, the goal is to ensure that individuals with disabilities, especially youth with disabilities, have *access* to supported or customized employment opportunities.

Effective July 22, 2016, individuals with disabilities cannot continue to be employed at a subminimum wage rate regardless of their age, unless the 14(c) entity (generally a sheltered workshop) has received documentation that individuals with disabilities have completed certain requirements. These include as follows: (1) Individuals who have been participating in subminimum wage prior to July 22, 2016, must complete a Career Counseling Information and Referral Services Course by July 22, 2016; (2) individuals who started participating in subminimum wage after July 22, 2016, must complete the course at approximately 6 months and again at the end of the year (this group requires two trainings in their first year and annually thereafter, and this course cannot be provided by the sheltered work staff); (3) the 14(c) employer is accountable for maintaining the needed records of the courses and asking for additional classes when needed to meet the guidelines.

For persons with Prader-Willi syndrome, the outcome of these changes is apparent. People with Prader-Willi syndrome have been frequent attendees of sheltered workshops using subminimum wage payments to provide competitive assembly work. The individual working and earning sub-minimum wage will find less and less work opportunities of this type. For example, 40 percent of sub-minimum wage providers in Florida have given up their certificates. Most of these providers are no longer providing paid work opportunities for their attendees. During this transition individuals are being given education regarding other work opportunities, many of which are not realistically accessible or safe for individuals with PWS. Families must be prepared to work for the evolution of a vocational service that is safe and rewarding and one that many parents can support.

The COVID-19 pandemic has opened many eyes. There are many new health and safety requirements now in place for the providers who survived. Many providers closed their doors permanently. Predominantly closures affected sheltered workshops. Many individuals who attended these programs have been unemployed and essentially "sitting home" for as much as a year. For people with Prader-Willi syndrome, this has caused and will continue to present challenges as they try to adjust to unemployment and as they seek new, and frequently extremely limited, employment opportunities. Transitions are sometimes difficult for people with the syndrome, and COVID-19, along with constant policy and reimbursement changes, is pushing constant transitioning. We must assess how we can make these transitions successful for the people we serve.

Advocacy and creative program development are what is going to solve the challenging future. The development of long-term support community placements is one solution for people with PWS. The supports for people with PWS need to be long term and built into placements as naturally as possible. Committees of experts will need to advocate for changes in funding mechanism, whether it be through the Department of Vocational Rehabilitation or state-based Medicaid waiver programs. Funding drives change and, in this challenge, it will be no different.

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Residential Care for Adults With Prader-Willi Syndrome

16

Mary Kay Zicardi

Introduction

For many families, the decision to explore residential placement for, and with a family member with Prader-Willi syndrome (PWS), is an overwhelming and emotionally charged task. People with PWS and their family face extraordinary challenges throughout life. One of the more daunting, yet critical, challenges is locating or developing a home that safely meets their needs, especially when attempting to predict and plan for services that may be required as an individual's needs change. Guidance from family and significant others, researching options and funding sources, and seeking experienced providers are critical elements in this decision-making process. Identifying the most pressing needs, both now and in the foreseeable future, will guide many of the immediate decisions in the search for, or creation of, a residential placement. Acknowledging and establishing the most critical components of care will lead people who need services, their families, and interdisciplinary teams to the best decisions possible.

Since the topic of residential options was explored in the third edition of this management book, much has changed. At the same time, the core program needs for most people with PWS that enable them to live healthy and fulfilling lives have remained the same. Small congregate settings, i.e., group homes, are no longer the *only* way, or even the *preferred* way, for individuals with PWS to receive the services needed to support a life that provides both the necessary structure and individual choice. For some, an apartment setting with a combination of natural (family), caregiver (paid), and remote (electronic monitoring) supports can provide the necessary supervision and services based on the individual's needs, safety risks, medical conditions, and time of day (or night). Others can be most successful while living in a home that is contained on the family property. This setting maintains autonomy while providing the security of being close to family. Conversely, some affected individuals thrive with more distance and are more successful living with others in another city or state.

Family members and other professionals who comprise the care team now realize that many environments can be modified to meet the care needs of the person with PWS receiving the services. Residential living options across the United States and throughout the entire world are increasingly diverse. Factors which may influence both the selection of a living option and the

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success of that selection include cultural and family values and beliefs, accessibility to funds and resources, and provider expertise and availability.

Small, community-based programs that provide supports only to people who have Prader-Willi syndrome can be successful using several different approaches. One example is a small (i.e., three to five person) single-family home that is blended into a residential neighborhood. Less common, though still in existence, is an integrated community-based home that supports five or more people. While there are many positives to a larger home, achieving this model has become more challenging as the demand for single bedrooms providing both privacy and space has become the expectation, not the exception. Although not universal, many earlier built homes for more than five individuals required two individuals to share either a bedroom or a bathroom. As care models have evolved, the expectation for greater individual privacy has also evolved. A strength of the larger residential model is that it promotes and capitalizes on peer relationships along with community presence and belonging, yet provides the environmental structure and treatment needs which the syndrome demands.

Some individuals with Prader-Willi syndrome are best supported in a segregated program on a large, campus-like setting, where an individual's rooms are in a cottage- or dorm-style building on the grounds. Many children and adults who live in this type of setting attend school or a vocational training program located on the campus; others are enrolled in school or work settings in the community. In this type of program, services are also provided on-site that address exercise, nutrition, activities of daily living, and behavioral supports.

By necessity or choice, some people with Prader-Willi syndrome live in homes with others who do not share the same diagnosis. While occasionally a family or individual selects this living arrangement, too often this residential option results from the necessity for an emergency placement when no segregated programs exist or are readily available. This arrangement presents particular challenges for those with PWS as well as for those with whom they live who have other developmental disabilities. While this living situation may indeed be successful for some, significant attention must be paid to food access as well as the unique privacy and property issues and behavioral challenges of the individuals with PWS while at the same time accommodating the less restrictive needs of other residents.

Locating or creating the brick-and-mortar home that is prepared or willing to implement a program to manage the uniqueness of PWS is a significant hurdle, and not one to be taken lightly. What occurs while in the program will define the health, safety, happiness, and quality of life for the individuals who will make it their home. Successful residential programs for individuals with PWS will have thoughtfully addressed and have plans to minimally meet at least six critical components of care: (1) structure and predictability, (2) specialized and secure environments, (3) supervision, (4) food security, (5) medical and behavioral management, and (6) competently trained caregivers [1]. This chapter reviews each of these elements so that those seeking placement for their family member can be aware of the best practices in each of these areas and can be equipped to make sound educated choices. In addition, we provide a set of questions that a parent seeking placement may want to ask of a potential provider. We also provide a set of questions for providers who are considering providing services to an individual with PWS. These can be copied and used as needed.

That being said, the family's full participation in, and disclosure of, their family member's strengths and needs is the first step in securing a successful residential placement. A residential provider has a significantly improved chance of meeting the individual's needs if all difficulties are discussed honestly and openly. Many willingly provide the necessary environmental modifications and behavioral accommodations to facilitate a lasting placement that includes a clinically sound approach to treatment and maintains an acceptable quality of life with positive outcomes. Especially if planning an initial placement, all team members, especially those outside

of the family, must be encouraged to openly and fully disclose all knowledge of the individual's strengths, weaknesses, and needs. This honest exchange of information will significantly improve the team's capacity to create and execute an environment and care plan that is lasting, healthy, and successful.

The prospective provider and family will be most successful for the individual if an open spirit and cooperative, respectful communications are established early in the relationship.

Required Components of Care in a Residential Placement Setting

Structure and predictability Individuals with PWS require – nay, *demand* – structure, predictability, and consistency, in all areas of functioning. Having the ability to know what will happen next is critical to reducing the pervasive anxiety prevalent in individuals with PWS. This can be manifested by persistent questions needing to know what is going to be served for dinner in 3 hours, what staff will be coming in to work for the next shift, or which parent will be coming to do pick-up for a weekend visit. It is not helpful for a well-intentioned staff or relative to say, "Why does it matter?" or "Don't worry about it" as that dismissiveness may potentially increase anxiety.

Just as the predictability need will vary across individuals with PWS, and will vary across time within each individual with PWS, so too how that predictability needs to be managed will be different for each individual. An experienced provider will be prepared to suggest strategies and support methods that create a sense of trust and security. While the goal may be for the individual to use concrete tools, i.e., calendars, visual schedules, notes, and emotional tools such as comfort-inducing key words, it is the role of the caregiver to teach and *encourage* the use of such tools until they are incorporated by the individual – or indefinitely if necessary. A structured and predictable environment will help reduce anxiety which ultimately will have a positive impact on the frequency and intensity of serious maladaptive behaviors and incidents.

Specialized and secure environments Whether seeking to live alone or with others, a needs assessment can help a team anticipate and create programs that address environmental risks. In all homes where individuals with Prader-Willi syndrome reside, food *must* be locked to prevent food access, maintain overall health, and prevent unwanted behaviors. Other considerations for items that may need to be locked are knives, trash, medications, and cleaning products. Since most state's regulations and preferences in the development of new programs now dictate that roommates sharing homes have their own bedrooms, it may be very beneficial to have locks on the bedroom doors and teach the occupant to carry a key and to lock their door when not in the room.

When considering an environment that will properly support some of the specialized physical needs for people with Prader-Willi syndrome, there are several other areas to be examined. It has proven very helpful to have a designated place for exercise in the home, complete with exercise equipment and an open space for walking or dancing. When possible, this area could also double as a movie or game room, i.e., an additional living space if there are multiple people sharing the home. A Jacuzzi-style bathtub with circulating water can be therapeutic to assist with the healing of open wounds, such as those resulting from skin picking. When searching for single-family residential homes, one-story ranch-style dwellings seem to be a preferred choice as stairs may present challenges to an aging population of people with PWS.

Supervision When an interdisciplinary team is determining the best available living situation and compiling the essential elements for the home, as before, a thorough needs assessment will assist to determine the required supervision levels.

It is a safe assumption that the person with PWS proposed to receive supports will require some level of supervision. Currently supervision needs are categorized as those needed during awake hours, those needed during sleep hours, and those needed during community outings and events.

If living with others, a consideration of all of the residents' needs must be factored into a determination of the necessary "staff-to-resident ratios" necessary to meet the needs of all. Special assessment tools are available that incorporate multiple individual needs in determining the necessary and safe staff-to-individuals ratio.

Additional supervisory decisions for awake times often need to be considered and negotiated. For example, one issue that often arises is whether a staff member should work with the same person(s) through the entire shift or is it best for all staff to interact equally with all of the individuals. This is likely best answered by each program individually but must be considered, particularly when working with individuals with PWS who can become overly attached to and possessive of "their" staff.

Overnight staffing issues present an additional set of decisions. Specifically, does the needs assessments indicate that the resident needs the staff to remain awake throughout the entirety of the night shift or is sleep during some part of the shift a viable option? While it may seem both obvious and common sense that this question and that of daytime staff-to-individual ratios required for optimal care are some of the most critical questions, what may not be so obvious is the need to assure that these critical decisions are *based on the service needs of the residents and are not made based solely on funding*. How these decisions are made can inform families and other team members of the decision-making principles that may be applied when other critical decisions arise.

The final issue for serious consideration when contemplating supervision needs involves community activities and events. While individual needs assessments may provide some insight into planning for community events, the assessment cannot determine the entirety of the answer. Of equal concern is "Do the housemates participate in community activities and events alone with just a single staff, or do they like to go out in pairs or small groups, and if so, how many staff are best?" Each person and event is different, and residents should have their preferences honored to the extent possible regarding going alone or with a housemate or two. The type of event, whether shopping, exercise, a small community festival, or a large sporting event or concert, will certainly drive some of the decisions about the number of people who can attend at one time and the number of staff needed to provide safety for everyone. An assessment can't always tell a caregiver all that needs to be known. Prior experiences are often the best teacher, and past situations shared by others may inform the interdisciplinary team whether or what changes in supervisory ratios are needed.

Food security Until there are pharmacologic interventions for the hyperphagia and food-related behavioral concerns for those with PWS, it is non-negotiable that residential program planning for individuals with Prader-Willi syndrome *must* include food security. And even the best made plans that include food security will present challenges if not executed with consistency. Again, knowing the support needs of the proposed resident is *key* to creating just the right level of secure environment. While the environmental aspect of securing food needs to be considered and addressed (e.g., will the entire kitchen be locked or only the refrigerator and the pantry?), equally important is how confident the individual with PWS feels about the level of food security.

Providers who are successful with food security often quickly understand that two of the most basic questions asked by individuals with PWS are "what" and "when" questions; "What am I going to eat for (*insert next meal/snack here*)?", "When am I going to eat?", and "Are you sure?" The need to have these questions answered combines two of the important components to be considered when searching for or creating a residential option – that of providing food secu-

rity in a structured and predictable environment. The "what" and "when" questions can be answered relatively simply, depending on the learning style and preference of the person(s) being supported. In many small group living situations, the meals and snacks are written on a dry erase or bulletin board and updated at regular intervals. Some individuals with PWS prefer to have their menus personally provided in paper format, others prefer email, while others may need to have menus provided in a picture format or verbally reviewed. The "when" question is usually answered by the structure of the daily schedule that documents when meals and snacks occur in the daily routine. This constant assurance usually provides sufficient security that the meal or snack will be available at the designated times.

Some people with PWS also need to know the "who" and the "how" to feel comfortable with the food security in their home. Who will purchase the food? How will it get to their home? There are as many methods for meeting these needs as there are provider agencies assuring it gets done. How these questions are answered – by what method and how often – need to be decided by each agency, with the best interest of the person's need for food security in mind at all times. Again, consistency is key.

Food security extends beyond what happens in the home. It is recommended that the team thoughtfully discuss options prior to community outings, school and work days, and social and family events where a meal or snack may be part of the activities. Just as the lack of a structured and predictable environment can lead to increased anxiety, the anticipation of an opportunity to obtain (additional) food can also lead to anxiety that may ultimately be at the root of a negative behavioral incident.

Food security can present many complex challenges, some that even seasoned providers may not anticipate until an incident occurs or a situation presents itself. Nonetheless, it is critical to openly assess each new environment and look for loopholes while providing emotional security via truthful answers to people with Prader-Willi syndrome.

Medical care and supportive services The complexity of individuals with Prader-Willi syndrome demands that residential providers and families work cooperatively to secure, periodically train and develop, and further nurture ongoing relationships with both medical and behavioral professionals that can enhance the quality of life for the people being supported for many years.

Locating, informing, and working cooperatively with physicians is often the responsibility of the residential provider. In cities that offer residential services for individuals with PWS where there is also a university or a large hospital with a center for genetics, there may be physicians who are knowledgeable, experienced, and well-versed in treating the complex needs of the syndrome. Unfortunately, this is the exception rather than the rule. More often, the provider and family must work to develop relationships with physicians willing to provide primary care, as well as those who have expertise in endocrine, gastroenterology, orthopedic, psychiatric, dental, podiatry, and a broad range of other necessary and specialty needs.

A residential program's provision of nursing, dietician, and exercise physiology supports plays key roles in the ultimate success of the individual's ability to achieve their health goals. The role each of these specialists provides in educating the residential staff as well as community members is invaluable and helps create safe, healthy, and enriched lives of people with Prader-Willi syndrome.

A nurse, employed by the residential provider, can have a positive impact on the relationship between physicians and the individual who requires medical care. In addition to ensuring that the required regulations for each state are met, the nurse can be the "eyes and ears" for the physicians. The nurse's knowledge of Prader-Willi syndrome and familiarity with each individual, combined with well-honed assessment skills, may save unnecessary trips to the physician's office. Although faced with many significant medical conditions and risks, people with PWS also regularly create or embellish medical com-

plaints. A skillful nurse can assist the physician by decreasing time spent on feigned somatic complaints, thereby assuring proper care for true areas of need.

An approachable, informed dietician is essential to create menus, discuss food preferences, and determine what food items are permissible for special occasions. In addition, when several people live together, each may have different caloric requirements. A creative dietician can assemble menus that are tasty and healthy and follow the physician's prescriptions. The successful dietician will be well-versed in all aspects of Prader-Willi syndrome. While such knowledge is essential for providing the appropriate menu, it is also essential for avoiding potential manipulations by the individuals with PWS regarding their diet plans. Further, it is beneficial that staff receive training related to the food aspects of the syndrome directly from the dietician. This training can include basic dietary guidelines and requirements, discussion of specific diets, practice with weighing and measuring portions, and role-playing on how to address the inevitable "what-ifs." Staff armed with knowledge and confidence are more likely to make competent and reasonable decisions when unusual situations present themselves. While a dietician may not always be immediately accessible, the training that a staff has been provided may enable them to alleviate the immediate concern until official clarification is obtained.

Additionally, a dietician may make regular visits to the home to monitor weights, make necessary caloric modifications, and adapt menus. Since food is of utmost importance to the person with PWS, a strong relationship with the dietician may help to provide assurance that the prescribed diets are indeed being followed.

An exercise physiologist or personal trainer also has a major role in a residential program. At the onset of a new program, the exercise physiologist must assess the individual's overall status. Once completed, an appropriate individualized exercise schedule can be developed. Periodic review of progress and necessary modifications in type and amount of exercise can help individuals achieve weight loss goals safely. Similar to the nurse and dietician, the exercise physiologist and/or trainer should play a supportive role to the individuals and a coaching and teaching role to the direct care staff who have the daily job of carrying out the plan. This can be achieved by answering the staff's questions about therapeutic exercise and supporting staff in their quest to encourage the individuals with their required exercise regimen.

In addition to physical medicine, many residential programs in which people share a living environment have found that a psychologist, social worker, or behavior specialist who has had training and experience in the unique characteristics of people with Prader-Willi syndrome is invaluable in supporting the interdisciplinary team. These professionals primarily assist in three ways: (1) assist with establishing a basic set of house rules; (2) develop, author, and oversee a positive behavior support plan; and (3) provide 1:1 counseling support to residents with PWS.

Establishing house rules The designated behavior professional can assist with establishing a basic set of house rules which, when equally applied to all, will set baseline standards for acceptable commonsense courtesies for all housemates. Depending on the structure and unique considerations of the residential situation, some examples of house rules may include the following:

*Keep your hands and feet to yourself.
*Leave the room when asked.
*No food is to be brought into the home.
*No trading, loaning, or borrowing items.
*Keep your bedroom door locked at all times.
*No leaving the house without a staff member

Not only does this team member play a key role in creating the house rules, they need to be attuned and receptive to input from everyone in the home to ensure that the house rules support and sustain a harmonious household of roommates.

Developing, authoring, and overseeing a positive behavior support plan A psychologist,

social worker, or behavior specialist who has been trained and is experienced in working with people Prader-Willi syndrome can lead and assist an interdisciplinary team by developing, authoring, and overseeing an individual behavior support plan, when one is needed.

Behavior support plans must be individualized and must address the unique and personal needs, strengths, and desires of each person. Developing positive behavior support plans for individuals with PWS often presents particular challenges. For example, a young lady with PWS was once overheard to say "we don't do something for nothing!" Historically, reinforcers used to develop support plans have often been food-based; since food-based rewards are off-limits for those with PWS, creating a response to "we don't do something for nothing" may require real creativity. While it may indeed be a challenge to identify potential non-food-based reinforcers for the resident with PWS, it is not only possible, it is the responsibility of caregivers to do so. When based on an individual's overall cognitive abilities, and especially designed to help the individual understand cause and effect (i.e., if I do X, then Y will occur), an individualized behavior support plan that offers not only rewards but also formalized structure, planning, and predictability may enable a person with PWS to live his or her best life.

Providing 1:1 counseling support The psychologist, social worker, or behavior specialist may be able to meet individually with people in the program. These sessions could be to provide counseling, address specific goals, or to work together on another project. Experience has shown that having an appointment time that is one-on-one and is unlikely to be interrupted often becomes a very coveted part of an individual's weekly schedule.

Competently trained caregivers People with Prader-Willi syndrome present differently than those with other types of intellectual and developmental disabilities, and their caregivers need to be supported and uniquely trained. Initial and ongoing training for staff is one of the cornerstones of building a residential program that maintains and promotes healthy, safe, and productive lives. At a multinational conference of residential providers [1], it became overwhelmingly clear that a cohesive, well-trained, and supported group of staff who are working towards common goals for people who have PWS has a significant and positive impact on the quality of their residents' lives. The participants also concluded that a staff's ability to grasp and demonstrate the required practical knowledge and the ability to show empathy and compassion are key to the success and happiness of the person receiving care. A consensus document of ten key points for achieving a well-trained staff were developed and have been adopted internationally (see Table 16.1).

Untrained staff can be dangerous to residents with Prader-Willi syndrome as well as to other staff. When individuals with PWS perceive the staff is unsure about proper management, their

Table 16.1 Consensus statement regarding training of staff working with individuals with Prader-Willi syndrome

People with Prader-Willi syndrome present differently than those with other types of intellectual and developmental disabilities; their caregivers need to be supported and uniquely trained. Initial and ongoing training for staff is one of the cornerstones of building a residential program that maintains and promotes lives that are healthy, safe, and productive.
There is no substitute for comprehensive training; it is essential.
Continuity and consistency between and across caregivers is critical.
Effective training avoids problems.
Training by both theoretical learning methods (classroom style) and applications (by others, on-the-job shadowing, coaching, and mentoring) is very important.
Training needs to be ongoing and introduce current practices and research.
Training is a strengthening and bonding tool for caregivers.
Agencies must listen both to people with Prader-Willi syndrome and their staff.
Staff must be supported.
The capacity for staff to work as a team is critical to the success of people with PWS.

sense of personal insecurity may increase, which is often accompanied by an increase in unwanted externally directed behaviors such as increased tantrums/meltdowns, attempted manipulation of staff, attempted triangulation of staff or other residents, increased arguments, overt jealousy, as well as personally directed behaviors such as an increased skin picking or other self-injurious or unsafe behaviors. Hazardous environments, such as unintentionally unlocked food and medication storage areas, may cause tempting and dangerous situations.

When preparing to train new staff, a key concept is that staff need to understand *why* training *specific* to Prader-Willi syndrome is important. Unlike other populations with which staff may have worked, it is critical that staff understand that Prader-Willi syndrome is a genetic condition wherein physiology often drives the behavior; specific behavioral responses may not always be a choice. Poorly managed PWS can be a life-threatening disorder or present behavioral concerns that raise safety issues for everyone. This requires that staff recognize that there are specialized approaches necessary for effective management of the resident with the syndrome. There are some approaches that, when used, may not only be ineffective, they may have the opposite effect of that intended and could also be truly harmful. For example, the use of "surprises" and spontaneity may be counterproductive due to the individual's need for predictability, security, and routine. Appropriately trained staff understand how to interact and that the combination of competence and confidence serves to reduce anxiety both for the resident with PWS and the staff member.

Beyond an understanding of why staff need to be specifically trained about Prader-Willi syndrome, the content of what should be trained in an initial and ongoing curriculum is critically important. A basic knowledge and general overview of the characteristics of Prader-Willi syndrome tops the list. This should include some core understanding of the genetic components, behavioral overview, nutritional and dietary needs, and menu plans that include meal management and food security. This should include the importance of exercise and weight management, hygiene, contributing to household maintenance, and medication administration rules. Training on the intense need to create and maintain a highly predictable and structured schedule must be included in any initial training of new staff. Further subject matters to be addressed initially must include the location of emergency contacts, the importance and systems of documentation, recreational and community activities, and vehicles and systems used for money management, to name a few additional areas.

Since staff usually spend the most hours with the resident with PWS, a frontline staff may be the first person who notices a change in someone's physical condition. It is imperative that any initial training contains content about urgent and significant medical risk factors, such as an inability to vomit, a high pain threshold, and a dysregulated temperature system that can decrease core body temperature and interfere with an elevated temperature despite serious illness.

Residential agencies must consider at what point in the overall orientation it is most effective to train the new staff regarding Prader-Willi syndrome. At the beginning of the work assignment, training may be most effective if it is conducted formally, intensively, and with purpose. This approach will impress on the staff that their training is of the utmost priority and not an afterthought. Most often, recommendations are made to train staff in two phases, beginning with classroom, theoretical information, and advancing to practical application of the theories through exercises such as shadowing and role-play exercises. It has also been reported helpful to assign seasoned caregivers to those newly hired to serve in the role of a mentor and teacher. Experienced and successful staff are the very best resources available.

How training is presented can also have an impact on the effectiveness of the staff's initial learning and retention of the material. Training that uses a variety of methods will likely be most

effective. Most trainers would agree that adult learners do best when in a safe and comfortable environment and the training session does not exceed 3 hours.

Inviting an experienced staff to lead a training session using anecdotes, humor, and role-playing scenarios that engage everyone can create invaluable and memorable training lessons. Training sessions also present great opportunities for building trust among caregivers via team building and playing games. Other successful training experiences worth noting are use of videos, providing independent reading, and study materials and lectures by contracted specialists, such as dieticians, exercise physiologists, and psychologists. After the core training is completed, the use of the biographies of the residents with PWS who have been served in the past to help illustrate real-life situations can be powerful learning experiences for both new and seasoned staff. Training completed in a classroom style setting is only the beginning of a staff's learning experience.

A great deal of the understanding about PWS is experiential once the new staff is working alongside others and learning the specific supports required. Finally, training sessions of any kind should include a post-training evaluation to obtain feedback from the participants about the effectiveness of both the training curriculum and the learning environment.

A staff's training is never complete as new opportunities for learning and improving skills present themselves every day. It is imperative to keep caregivers updated with new and advanced information and strategies throughout their work assignment. Staff meetings can also serve as training opportunities whereby new information is presented, real-time experiences are discussed and analyzed, and staff can be supported. The use of checklists for tracking training topics, further delineated by A (an urgent topic that a new staff has to know immediately), B (an important topic), and C (a topic that a staff needs to be informed about but is less important), is a valuable tool for training. It is considered a best practice for both the staff and the trainer/supervisor to sign the documents. Another effective training tool is a crisis checklist that can be used post incident as a "check off" for the discussion and critical evaluation of a caregiver's responses and actions.

Successful staff, along with their colleagues and leadership, have an obligation to build a comprehensive and engaging initial and ongoing training curriculum. Committing to this practice for every staff every day is a significant challenge facing residential provider agencies. Keeping current with advancements in understanding and developments in best practices in supporting people with Prader-Willi syndrome help assure healthy lifestyles which have gratefully resulted in people living longer, often outliving parents, thus requiring even greater reliance on the expertise of well-trained residential provider agencies. The challenge is for the agency's leadership and staff to continue to learn, grow, and support the needs of people with Prader-Willi syndrome with knowledge and compassion.

Putting It All Together

As previously indicated, selecting a residential placement for an individual with PWS is a significant decision and not one to be taken lightly. The substance and quality of what occurs while in the program will define the health, safety, happiness, and quality of life for the individuals who select this placement as their home. Successful residential programs for will have seriously addressed and have plans to minimally meet at least six critical components of care: (1) structure and predictability, (2) specialized and secure environments, (3) supervision, (4) food security, (5) medical and behavioral management, and (6) competently trained caregivers [1]. To determine as much as possible if this placement is the right fit for their family member, some of the questions that a family may wish to ask a potential provider include (Table 16.2):

Table 16.2 Questions families should consider when selecting a living option

General
1. How does the provider select and access physicians, ancillary medical services, behavioral consultants, etc.?
2. With permission, can the prospective provider share names and phone numbers of individuals and their families who currently use the agency's services and would be willing to be a reference for the agency?
3. How can I obtain a copy of the most recent licensing survey, if applicable?
4. Does the agency have any written materials about the services that we could take with us?
5. How long has the agency been in business?
6. What is the depth of the agency's experiences supporting people with Prader-Willi syndrome?
7. How does the agency handle an individual's finances?
8. Do you provide reports to the individuals and/or their families regarding their finances? If so, how frequently?
Agency staffing and consultants
9. Describe the hiring process used when selecting staff.
10. What initial and ongoing training does the agency require of staff?
11. How are direct support staff supervised?
12. What is the turnover rate for direct support and supervisory staff?
13. What is the average length of employment for a direct support staff at your agency?
Agency policies
14. How can a supervisor be contacted by a family during an emergency situation outside of normal office hours?
15. What contingencies are in place for medical and behavioral emergencies?
16. What issues are you mandated to report to parents/guardians?
17. What are your agency's policies regarding medication and its administration?
Program issues
18. How does your agency individualize services to meet varying needs?
19. How many people have you discharged from your program in the past year? Regarding those who had Prader-Willi syndrome, in general terms, what were the reasons for the discharge(s)?
20. What recreational, religious, and social activities are available? Are the opportunities for participation individualized, accessible, and consistent? What happens when an individual chooses not to participate when the rest of the group plans to go?
21. What kind of transportation is available for the individuals' use?
22. What is the agency's relationship with neighbors and the community at large? Describe how the individuals belong and have a community presence.
23. What is the agency's grievance procedure for the individual's and/or their families?
24. What is the frequency of your communications with families? What if my family wants to know more/less than the standard?
25. What is your agency's relationship to the individual's school or vocational programs? Can or will it change based on my family member's individual needs?
26. What is your agency's policy on visitation? Can families visit unannounced? Would we have a private place in which to visit?

Source: Adapted from C. Norwood, What Questions should I ask" Center for Mental Retardation. 2002 [2]

While not inclusive, this list can also provide a stepping off point in seeking and sharing information that may result in a positive, long-term relationship between the individual receiving support, involved family members, and the provider agency. Asking and discussing these questions with a potential provider agency can greatly assist in determining if the agency's program is indeed a match for the needs of the family member's needs. Further, any potentially contentious issues can be openly and thoroughly discussed.

Providers will also have specific information they may need in order to determine if they can provide a program that maximizes the health, safety, happiness, and quality of life for the individual seeking a home. While the list of topics below is not inclusive of every issue that a family and provider will encounter during their partnership, it does represent many of the most common questions that do require addressing prior to a family and provider entering a caregiving relationship. Many times, having knowledge in advance will alleviate any misunderstanding when a question or problem arises. While these questions can be used in an interview format, they can also be utilized conversationally by everyone as reminders of items that need to be discussed in advance, outlining and solidifying expectations of both the family and the provider (Table 16.3).

Table 16.3 Questions providers may consider when offering a living option

General
1. What is your family's goal for this placement? Are you seeking a permanent independent home for your family member, or do you consider this more as a respite setting?
2. What assistance, if any, would your family like or need in preparing for the move and transitioning your family member to the new home"
3. If an individual/family is considering selecting your agency, is there a list of references that may be contacted from others that currently receive supports?
4. How can a family obtain a copy of the most recent licensure/certification/compliance survey, if applicable?
5. Can the agency provide written materials about their programs, specifically the Prader-Willi program, that the family can have or access online?
6. Overall, how long has the agency been in business supporting people with developmental disabilities? Specifically, what is the length of the agency's experience supporting people with PWS?
7. Describe the agencies hiring policy, initial and ongoing training of all staff, and the specialized training for those new employees working in a PWS program. Clarify whether the family would expect to have input into the agency's hiring decisions.
8. Describe the average length of employment for both direct care staff and supervisory staff.
Communication issues
9. Discuss current primary care and specialty physicians involved with the person's care. Will the family and the provider work together to continue with the current healthcare team or agree to changes? Who will have primary responsibility for scheduling and accompanying the individual to the appointments, the family or the provider? What contingency contacts are in place for medical and behavioral emergencies, both for the family and agency?
10. How can a supervisor/management team member be contacted by a family member during an emergency outside of typical work hours? Discuss the same for family members – what situations would the key family members want to be contacted during their own workday? While we know all situations are not predictable, families and providers having a general understanding of the nature of these events will be helpful.
11. For what issues/incidents would you want to be contacted immediately? What is the best manner to reach you?
12. Do you prefer written communication from the agency staff? Barring major incidents how often would you like an update?
13. What are your preferred days and times for meetings?
14. What are your expectations of how conflicts will be resolved?
15. Does the agency have a formal grievance procedure? Provide a copy to the family.
16. Are there family members with whom the person to receive supports should not have contact and in what way, i.e., by phone, a visit in their home, or to leave the home with them? Who may visit in the home, and who may pick up the resident for outings or trips home?
17. Technology has presented multiple opportunities but also risks to safety. It is recommended that providers and families discuss in advance their expectations and "ground rules" for amounts of privacy related to cell phone access/usage, Internet, carrying money/access to debit/credit cards, online shopping, and unsupervised opening of packages received in the mail from people unknown to the family or provider. There are a wide range of opinions and values that are best sorted out and agreed to by each interdisciplinary team prior to any supports and services being initiated.
18. What type of transportation does the agency provide, and how readily available is it, or is it shared between multiple programs, for example? Does the family expect that the agency will provide transportation to and from the family's home for all visits, and if so, is this possible and permitted?
Program issues
19. What are your preferred methods of managing the behavioral manifestations of Prader-Willi syndrome exhibited by your son/daughter?
20. What interventions have been consistently successful with your son/daughter? What other interventions have been attempted but proven unsuccessful for your child?
21. Are you using a behavior support plan currently?
22. Should extended family visitation be used as a reinforcer for your child?
23. Do you have a relationship with your child's current educational/vocational staff?
24. Does your son/daughter have a religious affiliation? Which church/synagogue does he/she regularly attend?
25. How will your child's prescription medications be secured, if necessary, and administered during a visit to your home?
26. During visits to your family home, would you like to have menus and/or food packed to assist with nutritional management?
Finances
27. Will the residential agency serve as the individual's payee? Whether or not the payee, the family, and agency should discuss the agency's policies and practices on how individual's funds are handled, i.e., bill paying, cash on hand, etc. What role does/can the family have in finances, and what can the family ask to use funds for if the provider is the payee?

Summary

Many people with Prader-Willi syndrome will face significant challenges and difficult decisions throughout their entire lives. Deciding on the appropriateness and type of residential supports is one of the most important considerations facing any person with the syndrome and their family. Guidance from family and significant others, research of options available from well-vetted and respected national sources, and seeking answers to probing questions will greatly assist with making the best decision possible. Long-term successful residential programs, equipped with the foundation to manage and support the unique needs of people with Prader-Willi syndrome, have continued to be developed. It will only be through the relentless and collaborative efforts of both parents and professionals that all people who desire a personalized, yet safe, home where a quality of life can be achieved for everyone who strives to attain it.

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17 Inpatient Crisis Intervention for Persons with Prader-Willi Syndrome

Linda M. Gourash, James Hanchett, Janice L. Forster, James Loker, and Mary Cataletto

Development of the Obesity Crisis and Obesity Related Complications in Prader-Willi Syndrome

With correct management, large numbers of persons with PWS never become obese. Nevertheless, obesity and its complications remain the primary cause of morbidity and mortality for persons with the syndrome [1]. When environmental control of food is inadequate, there is an unrelenting weight gain leading to morbid obesity. The reasons are twofold: Persons with Prader-Willi Syndrome have *exceptionally low caloric needs* resulting from decreased muscle mass and a propensity for inactivity [2], and they have excessive calorie intake due to food-seeking behavior and hyperphagia. The latter is sometimes extraordinary.

The *clinical presentation* of a medical crisis due to obesity in PWS has been delineated from a large number of patients with PWS (human growth hormone naïve, with a few exceptions) arriving with various degrees of severity of cardiopulmonary compromise at the Children's Institute of Pittsburgh, which operated an inpatient rehabilitation program dedicated to PWS for roughly 30 years, providing an institutional memory for the full range of patient presentations and experiences with hospital management of an estimated 1000 or more individuals in medical crisis. While treatment with HGH may modify the progression of this process as described here, it clearly does not prevent it.

Respiratory causes account for 38% of deaths in the PWS population [3]. Persons with Prader-Willi syndrome are at high risk for sleep-disordered breathing (SDB) which includes hypoventilation and obstructive events [4–9]. These breathing abnormalities worsen with increasing obesity and persist in any individual who remains obese. In adults, obesity is defined as a body mass index (BMI) of ≥30 kg/m^2, while in children it is defined as a BMI greater than or equal to the 95th percentile for children and adolescents of the same age and sex [10].

Bolded words are defined in the glossary at the end of the chapter.

James Hanchett was deceased at the time of publication.

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Despite many warning signs, the seriousness of SDB and its pulmonary consequences often is not appreciated until there is a sudden critical illness, sometimes triggered by a respiratory infection, leading to prolonged hospitalization and disability. Persons of all ages including young children with Prader-Willi syndrome can die of obesity-related respiratory complications.

Because sleep-disordered breathing is common in PWS, a high index of suspicion is warranted in evaluating these individuals, particularly when considering procedures requiring anesthesia or sedation. Classic signs of sleep-disordered breathing such as snoring may not be present, and therefore a low threshold for sleep evaluation is recommended [11].

Obesity Hypoventilation Syndrome (OHS)

OHS is seen in non-PWS obese persons, but it is the exception and not the rule, while it appears to be the universal consequence of obesity in PWS and the presentation is quite different with ascending, nonpitting edema being an important clinical herald of the process in its early stages.

In typical persons, most patients with OHS will also have obstructive sleep apnea (OSA), with the majority in the severe range with an apnea-hypopnea index (AHI) $\geq$ 30 events/hr [12]. Patients with PWS with the same number of sleep-related respiratory events have more prolonged hypopneas and hypoventilation than is typical of OHS [13].

Persons without PWS receiving testosterone may have worsening SDB [12]. Full nocturnal polysomnography is recommended pre-initiation and post completion of testosterone therapy [12].

The mechanism of the OHS pathophysiology in PWS is not entirely settled, but it could be related to the syndromic abnormalities in musculature that contribute to obesity-related hypoventilation during sleep with ensuing ventilation/perfusion (V/Q) mismatch leading to sustained nocturnal hypoxemia. Abnormal ventilatory [14, 15] and arousal [16] responses to low oxygen or retained CO2 have been demonstrated due to dysfunction of peripheral chemoreceptors and/or defective afferent pathways to central controllers. **Hypoxia** has long been known to cause increased **pulmonary vascular resistance** [17]. At this point the effects of abnormal musculature again likely plays a significant role. Lymphatic return depends on muscle activity, and the additional pulmonary vascular resistance appears to be enough to produce a dependent lymphedema sometimes massive in severity. Over time the increased pulmonary resistance leads to right heart overload [17] which may further compromise venous and lymphatic return.

This sustained **hypoxia** is the typical pattern seen on sleep pulse oximetry of obese patients with PWS and is relatively uncommon in non-PWS obese persons [18, 19]. Oxygen saturations during wakefulness are initially less severely affected [12], and daytime hypoxia represents further serious deterioration.

The American Thoracic Society (ATS) 2019 general (non-PWS) guidelines recommend both polysomnography and a measurement of arterial blood gas during wakefulness to establish the presence of hypercapnia. Screening can be performed by measuring serum bicarbonate level in a venous sample and evaluating oxygen levels by pulse oximetry during sleep.

Early recognition and intervention are essential to preserve good health and to prevent permanent venous and lymphatic damage in the lower extremities, a common disability in PWS.

Signs of Medical Deterioration Due to Obesity

In PWS, the sequence of events leading to morbidity, disability, and death from **obesity hypoventilation** is fairly stereotyped and can be observed in reverse during rehabilitation. The sequence can develop over a period of months in the face of rapid weight gain and severe SDB or more gradually in patients whose weight is stable but in the obese range for many years.

- Stage 1: Asymptomatic nocturnal **hypoxia**.
- Stage 2: Subtle edema of lower legs seen with more extensive nocturnal hypoxia and some decreased exercise tolerance.
- Stage 3: Daytime **hypoxemia**; edema may be massive, palpable to hips or higher.
- Stage 4: **Hypercapnia** or **respiratory failure**; severe truncal edema itself may further compromise respiratory function.

Stage 1: Nocturnal Hypoventilation and Hypoxia

Obesity leads to abnormal breathing beginning during sleep. A maximum "safe" weight for obese persons with PWS has not been defined but appears to be something less than 200% of IBW (ideal body weight) based on the 50th percentile weight for height. It is possible that younger children tolerate obesity less well than adolescents and adults. **Hypoxemia** first appears during REM phases of sleep [4] and, as the obesity worsens, can be demonstrated throughout the night sometimes with profound and prolonged hypoxic episodes (Fig. 17.1). This finding is subclinical; that is, it is not evident unless detected by specific diagnostic testing. Simple all-night finger or ear probe pulse oximetry can be performed in the patient's home to detect the early stages of the obesity hypoventilation syndrome before it progresses. Full sleep studies are needed to recognize obstructive and apneic events, however, and are indicated where available.

Stage 2: Altered Cardiopulmonary Dynamics Manifested by Edema and Hypoxia

In the PWS population, **edema** is the earliest clinical sign of obesity hypoventilation; *it is frequently missed*. The reason for this appears to be the visual subtlety of edema in the obese child or adult with PWS. It is best appreciated with the hands rather than the eyes. One useful way to describe this type of edema is that the "fat gets hard" as the turgor (firmness) of dependent tissues increases. *Pitting is usually absent*. Tactile comparison (not compression) of tissue in the lower part of the body to the upper arm will demonstrate an increased density of the tissue. It will be possible to palpate the **nonpitting edema** in the lower part of the body to the level of the knees, thighs, hips, waist, or higher. This finding is not always as appreciable in children. In the absence of diuretic use, the level of edema correlates fairly well with the severity of **hypoxia**. Therefore, detection of a lesser degree of edema to the knees or thighs is especially valuable as an early sign of altered right-sided cardiopulmonary dynamics. These patients typically still have normal resting oxygen saturations during the day, but pulse oximetry

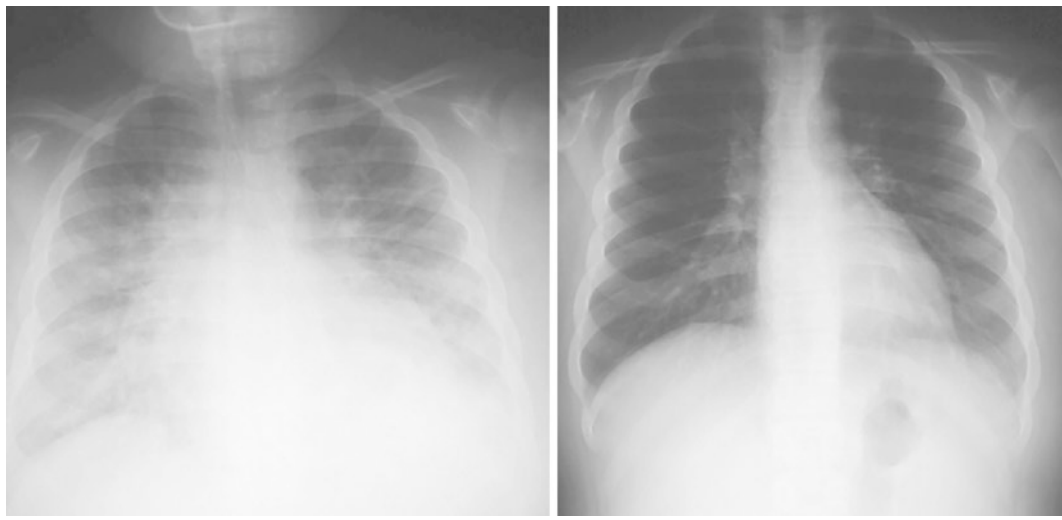

Fig. 17.1 A young patient had cardiomegaly on radiograph (left) which resolved to normal heart size (right) after 5 months of rehabilitation. Normalization of pulmonary hypertension was demonstrated by echocardiogram shortly afterwards

testing during exercise will sometimes demonstrate desaturation. In younger patients, children through young adults, in the presence of *any* recognizable edema, nocturnal oxygen desaturations are usually quite extensive. Older patients may have edema from other causes or from chronic lymphatic damage from milder degrees of sleep-disordered breathing. Decreased exercise tolerance is also a useful sign of early-onset obesity hypoventilation. Often, this is difficult to differentiate from the noncompliance displayed by persons with the syndrome. Families do not always perceive the symptom because young children are adept at appearing to carry out their usual activities while conserving their energy. Similarly, orthopnea (sleeping with extra pillows or sitting up) and symptoms of OSA (obstructive sleep apnea) are present only sometimes.

Stage 3: Daytime Hypoxemia, Edema, and Clinical Cardiopulmonary Compromise

Even in this stage, obese patients with PWS sometimes come to medical attention with only complaints of reduced exercise tolerance. Ambulatory patients with daytime oxygen desaturations often have **nonpitting edema** to or above the level of the thighs and hips. Extensive nonpitting edema to the level of the chest can still be subtle enough to be missed (Fig. 17.2), but other patients visibly display massive edema, especially in the lower extremities, causing secondary morbidity: weeping, cellulitis, and, most ominous, impaired ambulation. Some patients are sedentary and increased daytime sleeping may be a prominent symptom. Inactivity further impairs the quality of ventilation both during the day and at night in addition to increasing the risk of DVT. When the patient is awake and sitting quietly, oxygen saturations may be well below 85%, dropping lower still with activity. Cardiomegaly on chest X-ray sometimes still appears absent or "mild." As persons reach the stage of daytime **hypoxemia**, they will typically increase their resting respiratory rate, but this **tachypnea** >25/min is not readily appreciated since *it is generally not accompanied by a visible increase in respiratory effort*. Resting breath sounds are often barely audible with the stethoscope. With activity, however, increased respiratory effort is more evident and often reported by family members as shortness of breath.

Stage 4: Respiratory Failure

Respiratory failure with CO2 retention is a life-threatening condition which may be acute or chronic. Obese persons with PWS may continue to survive in a compensated state in stage 3 for years without evidence of respiratory failure *if* their obesity is stable and *if* they remain active. However, they will deteriorate eventually, or they suddenly may become critically ill when decompensation is precipitated by an intercurrent respiratory illness or following an orthopedic injury resulting in decreased ambulation. Clinical data clearly indicate that inactivity and overuse of oxygen therapy both cause worsening daytime and nighttime hypoventilation with increasing CO2 retention (see **Management**).

It also appears that some patients can progress to severe life-threatening cardiac compromise without evidence of **respiratory failure**. We have rehabilitated a number of patients from very late chronic *cor pulmonale*, and as long as the patient can be made to be ambulatory, and calories restricted so that weight loss occurs, the condition is usually reversible. Clearly the younger the patient and the sooner the intervention, the better the prognosis for full recovery from critical illness.

Management of Obesity Hypoventilation Syndrome

The fundamental pathophysiology of the OHS condition should be kept in mind in order to avoid mismanagement. Patients are hypoventilating, day and night. Underlying this is congenitally poor respiratory musculature. Adiposity thickens the chest wall thereby further restricting excursion (Fig. 17.3), and in some cases there is additional tissue stiffness with loss of compliance brought on by edema fluid as seen in Fig. 17.2. In sum, *the respiratory drive is inadequate to overcome the*

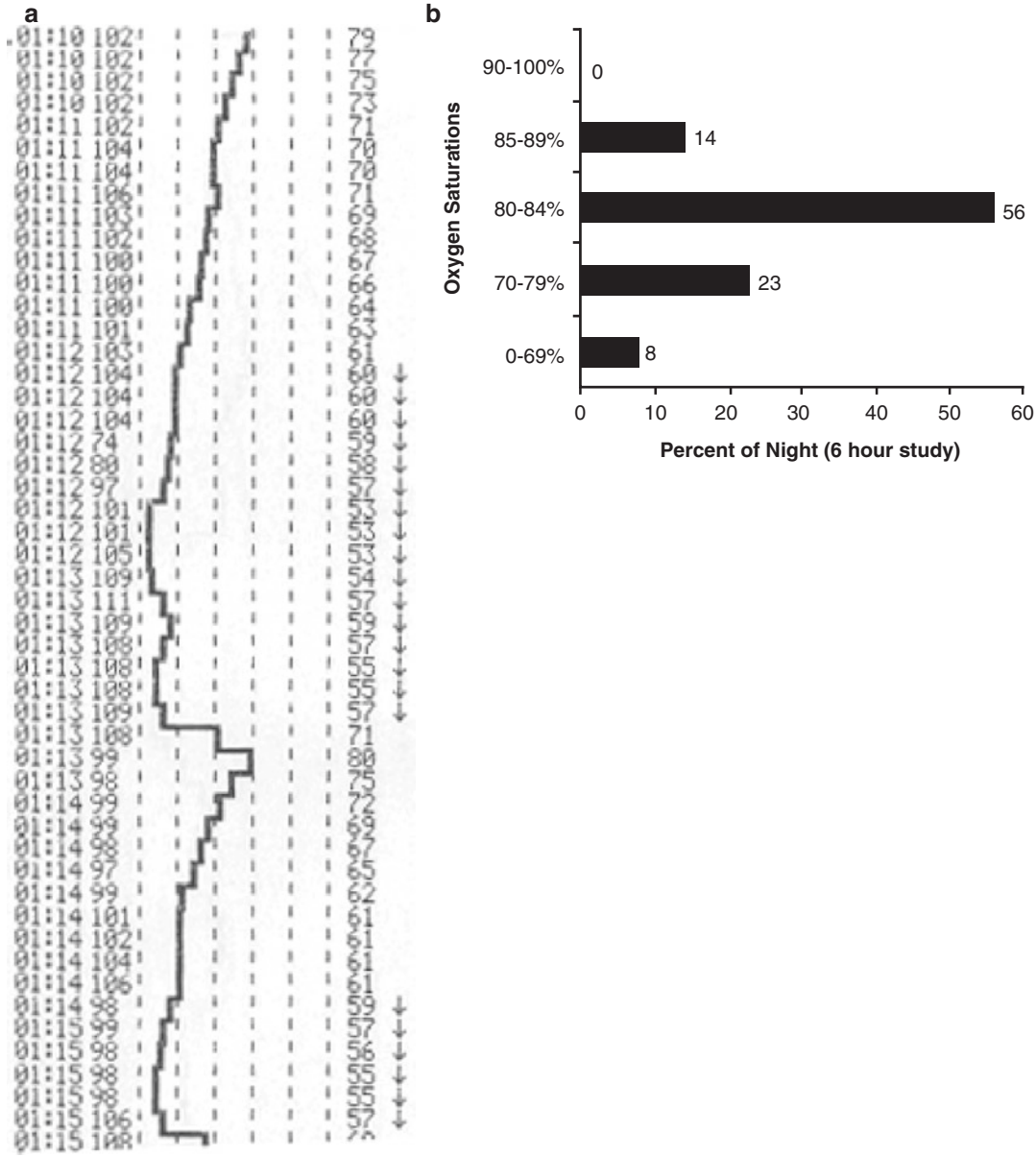

Fig. 17.2 (**a**) Pulse oximetry studies during sleep are very useful in identifying low blood oxygen in obese patients with PWS. These studies are relatively inexpensive and may be arranged at home while waiting for a formal sleep study. This 5-minute sample from a 6-hour study shows the severe hypoxia with oxygen saturation dipping below 60% (normal 93%–96%), which took place in a severely obese teenager who was only slightly symptomatic. She had mild shortness of breath with exertion and a subtle increase in tissue turgor of her lower body (fluid retention from early right heart failure). (**b**) The bar graph depicts the data from a 6-hour nighttime study of the same teenager. The graph shows that once asleep she spent the entire night with oxygen saturations below 90%, most of the night (56% of the 6-hour study) with oxygen saturations in the 80%–84% range, and 8% of the time under 70% (0%–69% range). These abnormalities in oxygenation may take place without obstructive or non-obstructive sleep apnea and are primarily due to poor ventilation leading to a V/Q mismatch. Hypoxia is sometimes overlooked on sleep studies because there are no "events" in the form of apnea or arousals

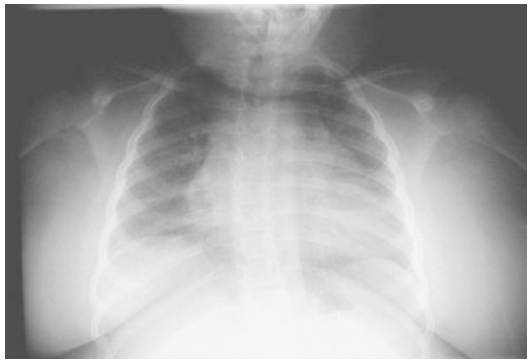

Fig. 17.3 This chest radiograph illustrates the thickening of the chest wall in a severely obese patient with PWS. Excessive subcutaneous fat changes the energy requirements for breathing, causing hypoventilation in obese persons with the disorder

increased work of breathing. Oxygen therapy, poor positioning, and inactivity worsen the condition of decreased respiratory drive.

Positioning

Ventilation is well known to deteriorate in the reclining position [19]. Very obese, edematous individuals may further compromise their own ventilation if the abdominal mass is resting on their thighs in a hospital bed [20]. Patients benefit from sleeping in a recliner rather than a hospital bed so that their legs can be supported from below on a footstool allowing the abdomen to remain sufficiently pendulant so as not to impinge on lung volume. These measures generally apply only to persons in stages 3–4 of obesity hypoventilation. Obese persons with PWS who prefer sleeping at night in an upright position (**orthopnea**) can be assumed to be in significant danger from their obesity.

Activity, Diet, and Spontaneous Diuresis

Two primary modalities are effective in reversing the cardiopulmonary deterioration of obesity hypoventilation. These are calorie restriction and ambulation. External ventilatory support (CPAP, BiPAP) is adjunctive, and difficulties with implementation should not distract from the more important ambulation and calorie restriction.

Daily intake of 600–800 kcal. will provide adequate nutritional maintenance in the obese, ill patient. In our observational experience, higher caloric intake is not needed even for wound healing of self-injury or decubiti. The reader is referred to other sources for details on how to present an attractive low-calorie diet for persons with PWS.

Rehabilitation to any higher level of physical activity is essential for recovery. Even the most seriously ill patients, if conscious, must begin this process immediately upon hospitalization. A physical therapy consultation should be the first order of business, regardless of the patient's condition.

Patients who are critically ill, edematous, and short of breath are understandably reluctant to move. The typical Prader-Willi behavioral traits of stubbornness and manipulation may now become immediately life-threatening when patients refuse to cooperate. Therefore, skilled therapists working in teams of two or three may be needed to initiate activity in a non-ambulatory patient (Fig. 17.4). **All other medical measures are supportive therapy and will not reverse the condition.**

Rehabilitation consists of gradually increasing demands for physical activity, beginning, if necessary, with walking only a few steps from bed to chair for meals. Because mealtime is an excellent motivator, *patients with PWS should NEVER be fed in bed*. Physical and occupational therapists are successful only when they have adequate support from family or nursing staff and adequate time to wait out the inevitable behaviors of PWS such as whining, crying, delaying, manipulation, and frank refusals by reluctant patients. Additional behavioral incentives implemented by the team may be required also. Verbal praise and stickers may be highly motivating; the use of food as reward is strongly discouraged even if calories are controlled because food for PWS patients must always be **noncontingent** to avoid anxiety-related behavior problems.

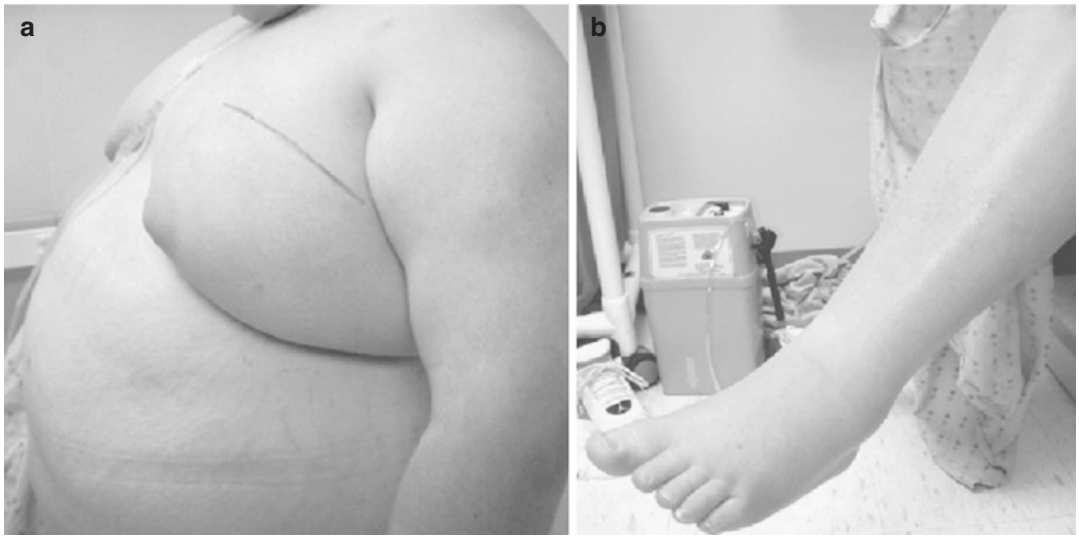

Fig. 17.4 (**a**) This young man with PWS had severe nocturnal and daytime hypoxia and palpable edema (increased tissue density) to the upper chest (marker line). (**b**) Lower extremity edema may not be visually impressive (same patient) and is easily overlooked

A total therapeutic milieu must be created around the patient both in and out of the hospital to facilitate this process. Family, nurses, and therapists will need to work together; consistent expectations and behavioral rewards may be implemented by nursing as well as therapy staff in consultation with a behavioral consultant, preferably someone with experience with PWS. As previously mentioned, the person with PWS should not be fed in bed. Initially, meals may be served in a table and chair by the bedside. Then by increasing the distance that the person must walk to and from the meal guarantees cooperation for physical exercise at least three times per day. As physical therapy demands for ambulation increase, meals can be scheduled after exercise sessions. This includes delaying (not cancelling) meals until modest therapy goals are achieved. Ethics guidelines or policies may need to be modified for meal delay to take place, but the intervention should be understood to be lifesaving.

Communication with the patient requires some skill and follows the guidelines at the end of the chapter to avoid nonproductive efforts.

Spontaneous Diuresis

Spontaneous diuresis of edema fluid and improving oxygen saturation are the hallmarks of recovery. The effects of a low-calorie diet and increased activity in producing a diuresis are at times dramatic (Figs. 17.5 and 17.6). We have seen this effect within hours of initiating physical activity and restricted calories, but it can also be delayed for weeks. There is a known natriuretic effect produced by low-calorie intake [21, 22], which together with exercise [23] and improved ventilation produces a physiologic response that marks the patients' return to improved cardiopulmonary function. Severely edematous patients have eliminated as much as 2 liters of fluid per day (without diuretics) during the initial stages of rehabilitation. In the absence of drugs that impair **renal** function (such as diuretics or topiramate), this rapid diuresis has not been associated with electrolyte abnormalities. Further, use of diuretics appears to delay this diuresis rather than assist it even if **azotemia** is avoided. Daily weighing is an extremely useful tool to track this response since urinary output is rarely something measured accurately in persons with PWS. Dieticians

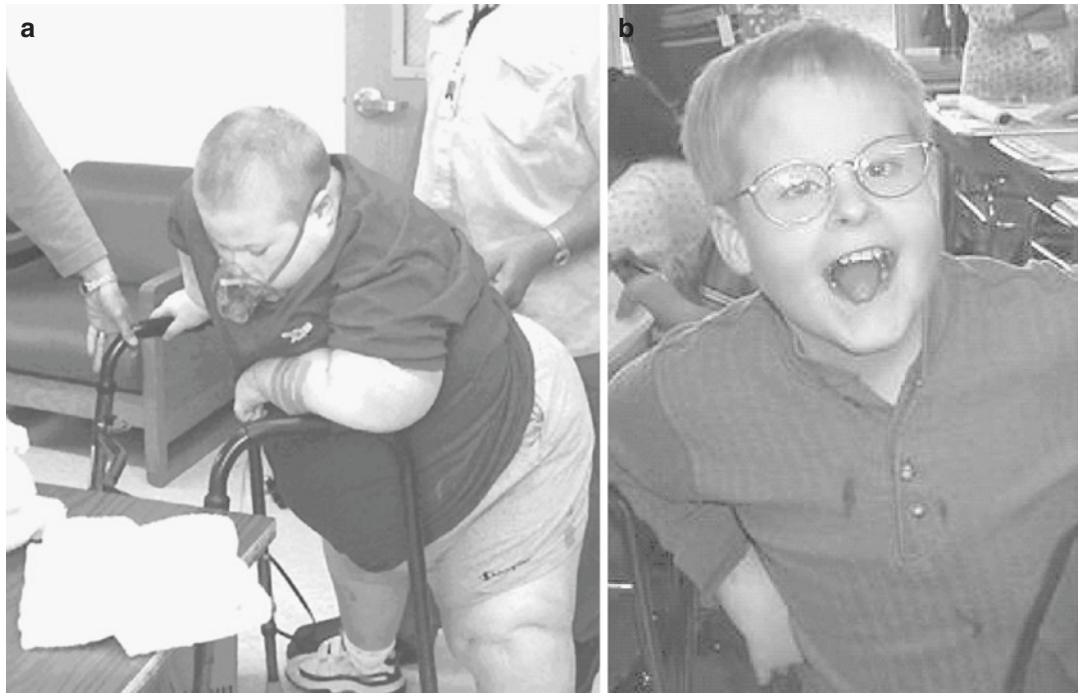

Fig. 17.5 (**a**) A 9-year-old boy with massive edema, profound hypoxia, and dangerous levels of CO_2 retention from obesity hypoventilation. Physical activity is an essential component of management and recovery, even in the critically ill patient. (**b**) Six months after presenting in critical condition, this same 9-year-old boy was active and healthy in school

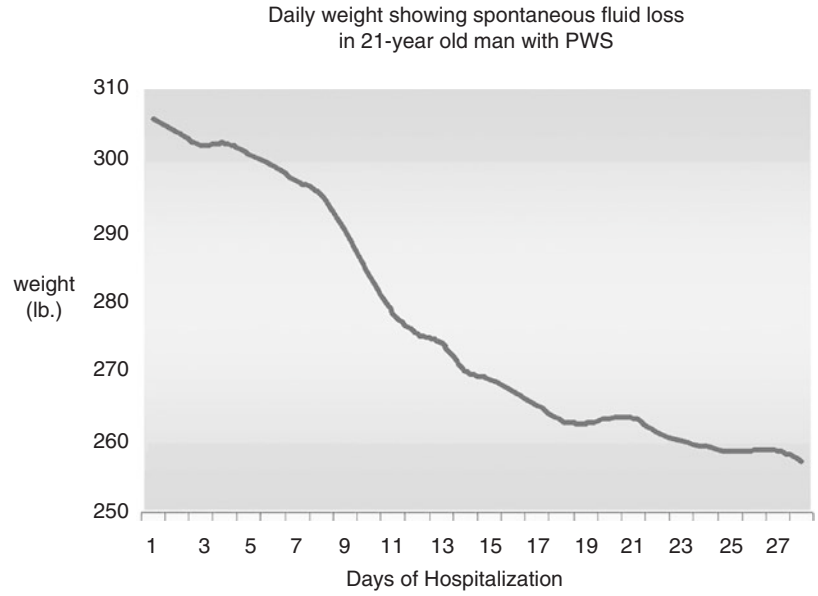

Fig. 17.6 This graph shows the daily weight measurements of a patient (pictured in Fig. 17.4), beginning at the time of his admission to a rehabilitation unit. He lost 48 pounds in his first 28 days of rehabilitation, with rapid improvement in his endurance and hypoxia. This massive *fluid loss* is achieved without the use of diuretic medications and appears to be a response to calorie restriction and increased physical activity, which improves ventilation

can sometimes be alarmed by the rapid weight loss and must be kept informed of the underlying physiology of the phenomenon lest they *increase* the calories.

Use and Misuse of Oxygen Therapy

In our experience, these individuals are at significant risk for CO2 narcosis and further respiratory depression if given amounts of supplemental oxygen (O2) sufficient to normalize oxygen saturations. The resulting respiratory failure can lead to respiratory arrest, **intubation**, and admission to critical care that rapidly produces body **deconditioning**, markedly worsening and prolonging this crisis.

Rather, in the edematous patient, **hypoxemia** may be assumed to be chronic (present at least at night for months or years) and need not be corrected too quickly. Extensive compensatory mechanisms that avoid tissue hypoxia have been documented [24]. Because it is generally true that, in a young person (without PWS) with **hypoxemia** and no lung disease, oxygen therapy can do no harm, oxygen is often given at high flow rates. **This is the most common error leading to iatrogenic death in extremely obese persons with PWS**. In our experience, hypoventilation gradually and subtly worsens over hours or days when patients are given more than 1 liter/minute of oxygen (24%) in the absence of ventilatory support such as BiPAP. Patients who are hypoventilating do not appear distressed; the only indication of excessive use of oxygen is dropping O2 saturations. Understandably many clinicians will, at this point, *increase* the rate of oxygen flow. This leads to worsening CO2 retention with lethargy and potentially a *respiratory arrest within minutes or hours*.

Patients in stages 3 and 4 appear to benefit from 1 liter/minute of oxygen without worsening their hypoventilation provided increased activity also occurs. Attempts to "normalize" oxygen saturations with oxygen therapy should be strictly avoided as the ensuing hypoventilation has been seen to be lethal. One liter of O2 per minute by nasal cannula generally raises oxygen saturations to high 70s or low 80s, and this appears adequate while rehabilitation takes place. Oxygen saturations will be lower during activity, and by our observation, this is neither harmful nor does it hamper recovery. Patients should have their electrolytes checked especially if they are on oxygen therapy. After 2–3 days on oxygen therapy, bicarbonate levels may rise as the kidneys produce a compensatory metabolic alkalosis. The usual carbon dioxide (CO2) combining power is 25 mmol/L or less, but in those with early CO2 retention, it is 29 mmol/L or higher.

This finding confirms a respiratory acidosis from increasing CO2 retention and is a valuable warning sign and tool in the absence of the availability of blood gases. **Furosemide and other diuretics may mask this effect**.

External Positive Airway Ventilation

External positive airway ventilation (**BiPAP and CPAP**) definitely improves nocturnal ventilation but sometimes delays definitive therapy if substituted for rehabilitation and weight loss. For stable patients who can be managed in the outpatient setting, continuous positive airway pressure (CPAP) is recommended with the goals of controlling sleep-disordered breathing and reversing awake hypoventilation [12]. While some have expressed concerns regarding adherence in adults with intellectual disability, there are both published and anecdotal desensitization protocols aimed at improving compliance [25, 26]. Sleep studies show improved ventilation, and some patients report more comfortable sleep with CPAP/BIPAP. It should be understood that many patients who have completely refused CPAP/BiPAP therapy have nevertheless been fully rehabilitated despite ongoing profound nocturnal hypoxia. Nocturnal ventilation usually improves (sometimes rapidly) once a physical rehabilitation is underway.

Use and Misuse of Diuretics

If used at all, diuretics must be administered with a clear understanding of their benefits and risks. In the presence of right-sided heart com-

promise, the edema fluid is a physiologic compensatory mechanism that serves to improve cardiac output by increasing right heart filling pressure. Excessive use of diuretics decreases intravascular volume with little impact on the **interstitial** edema of the lower body. Further, diuretic use risks the development of **renal** and **hepatic hypoperfusion**. Despite impressive dependent edema, **pulmonary edema** is not characteristic of the compromised patient with PWS, and OHS should not be cited as a reason to give diuretics unless *left* heart dysfunction has been established.

The doses of diuretics that produce azotemia also produce **hepatic ischemia** with rising levels of **transaminase**. Diuretics should be tapered, and **ACE inhibitors** and nonsteroidal anti-inflammatory drugs (NSAIDs) should be discontinued immediately.

The typical adolescent and older person with PWS who has not been on human growth hormone HGH or testosterone has a **serum creatinine** of 0.5–0.7 mg/dl, and if the creatinine is greater than 0.9 mg/dl, then **renal** hypoperfusion/injury should be considered.

Surgery

A recently published prospective observational study of 10-year outcomes of bariatric surgery in individuals with PWS showed lack of sustainable long-term weight loss or resolution of comorbidities [27], and a published and extensive review of the PWS literature offers the same conclusion [28].

PWS Medical Issues and Precautions

Some related medical issues in the obese patient with PWS require vigilance and management. Further, a number of unusual features of the syndrome can complicate care if not made known to the clinical team. Additional information is available in the Medical Alert Booklet available from the PWSA-USA website.

Leg Edema and Cellulitis

Leg edema in a person with PWS has been clearly linked to sleep-disordered breathing. Long-standing edema results in chronic tissue changes of the lower body including the legs and lower abdomen (Fig. 17.7). The resulting **venous stasis** and **lymphatic** damage predispose patients to chronic lymphedema, ulcers, **venous thrombosis**, and cellulitis. Intervention to prevent the prolonged condition of **obesity hypoventilation** is essential to avoid irreversible damage to the lymphatic and venous systems of the lower legs. There is no question that skin picking behavior of PWS, while not usually resulting in infection in other parts of the body, is a major contributor to episodes of leg cellulitis.

Direct pressure techniques to the legs or use of support hose appears to be of limited use unless part of a full protocol practiced by persons experienced in the treatment of either chronic or acute **lymphedema**. Support stockings are rarely helpful, ill-fitting, and frequently counterproductive causing pressure tissue breakdown or constriction of fluid outflow by bunching up or rolling up in the skin folds on the legs. Diuretics may give temporary reduction of edema but at the expense of poorer cardiac output. The fundamental problem must be addressed by increasing activity to mobilize edema fluid and caloric restriction producing weight loss.

Signs of cellulitis can be subtle as legs are often already chronically swollen, indurated, and discolored. A high index of suspicion and close daily examination and comparison of the legs by caregivers seeking changes in the *feel* or appearance is essential. Serial photos in good lighting may help identify changes over time. Patients do not always exhibit fever or pain. Most cellulitis, diagnosed early, can be managed with oral antibiotics sometimes in combination with an antifungal agent (such as fluconazole keeping drug interactions in mind). Preventative use of antibiotics is discouraged to prevent development of resistant strains of bacteria. Maintaining and increasing physical activity and leg elevation

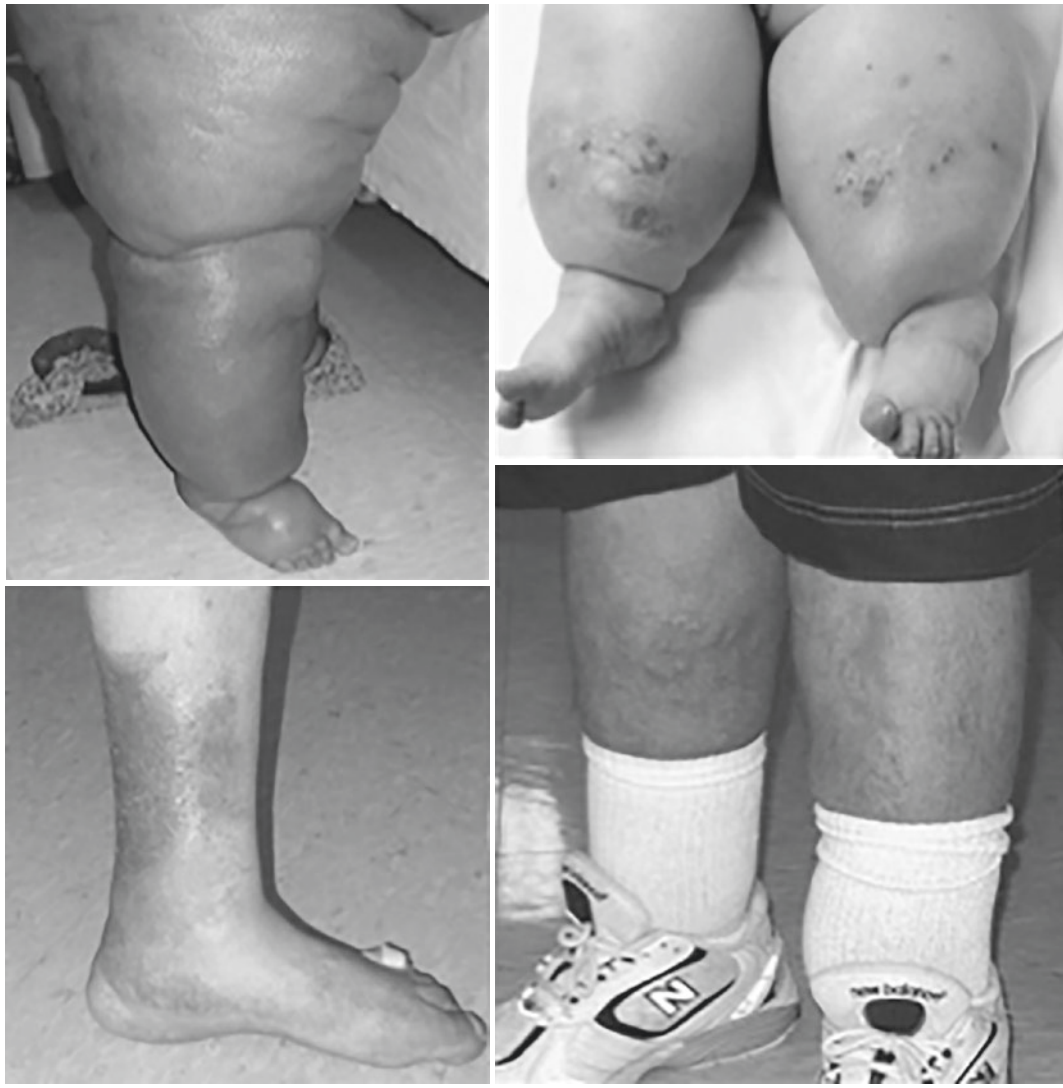

Fig. 17.7 While some edematous patients retain fluid throughout their subcutaneous tissue as in Figure 17.4, others demonstrate severe leg swelling. In either case, long-standing (probably 10 or more years) and often unrecognized obesity hypoventilation results in changes in the lower extremities that are irreversible and predisposing to cellulitis. These include dilated veins, damaged lymph vessels, and chronic stasis changes (hemosiderin discoloration) of the skin

when the patient is sitting have proven most useful for managing this very difficult condition. Cellulitis and superficial venous thrombosis are not reasons to limit activity; rather, the reverse is true. Patients who have ceased to walk for any reason are in real danger from **thromboembolic** events, and prophylactic anticoagulation should be considered. Rehabilitation to some level of ambulation is the highest priority.

Pulmonary Embolism (PE)

Pulmonary embolism is a type of venous thromboembolism in which the main pulmonary artery or one of its branches become obstructed. Most emboli arise from the lower extremity proximal veins, including iliac, femoral, and popliteal [29, 30]. Obesity has been identified as both a strong and independent predictor of pulmonary embolism [31].

A retrospective review of the 2017 PWSA registry identified pulmonary embolism as the fourth most common cause of death [3]. This was followed by a questionnaire survey in 2019 survey of 1067 individuals with PWS focusing on pulmonary thromboembolism, in which 33 adult cases were identified. Similar to the general population, obesity, metabolic syndrome, and renal and cardiopulmonary dysfunction were identified as predictors of PE. However, vasculitis was also identified as a critical feature and one that might be amenable to interventions to reduce skin picking and mitigate secondary infections of these skin lesions. Notably this study did not find a relationship between obesity and PE in children. Rather, when PE occurred, it was related to surgical complications or genetic factors related to family history. Growth hormone was associated with decreased risk of PE although the data is limited [32]. Further study by this group compared thrombotic events in obese patients with and without PWS and showed an increased number of thrombotic events across all age cohorts within the PWS population as compared to their obese counterparts [33].

The clinical presentation of acute PE is often nonspecific and, in some cases, may be asymptomatic. The scenario of shortness of breath, chest pain, near or actual syncope, or hemoptysis most commonly triggers evaluation for PE. PE may also be an incidental finding during an evaluation for an alternate diagnosis. For those with preexisting cardiopulmonary disease, such as can be seen in obese adults with PWS, worsening dyspnea can be a warning sign. **Hypoxemia** and **hypocapnia** are often present with acute PE. Diagnostic strategy should be based on clinical probability determined by clinical judgment or prediction rule. Therapeutic strategy is determined by risk stratification based on clinical symptoms and signs of hemodynamic instability [34]. PE in children is associated with deep vein thrombosis in up to 60% cases. Diagnosis can be delayed or missed with an average time to diagnosis of 7 days. Up to 16% of cases are asymptomatic. In those with symptoms, shortness of breath and chest pain were most common. Massive PE, while rare in children, is associated with a mortality rate of >50%. Multidetector CT-PA is now the preferred imaging modality, replacing ventilation perfusion scan because of its high sensitivity and specificity, wide availability, and short imaging time. The presence of a sharply marginated complete or partial pulmonary arterial filling defect present on at least two consecutive images using the multidetector CT-PA technique is diagnostic [35].

Hypoxemia associated with PE in persons with OHS is an especially dangerous situation because of the nearly universal tendency for medical personnel to respond with an aggressive attempt to fully correct the oxygen deficit with supplemental oxygen, potentially causing rapidly developing respiratory failure and respiratory arrest.

Diabetes

Elevated blood glucose and type 2 diabetes, seen in 25% of adults with PWS [36], are nearly always indicative of excessive calorie intake. In the vast majority of patients, normal **glycemic** control is restored when exercise and dietary control are implemented. The need for diabetes medication in increasing doses indicates a crisis with the patient's intake and weight. It is a temporary substitute for definitive intervention which is environmental, not medical.

Hypertension

Most hypertension in PWS is directly related to obesity hypoventilation and requires definitive intervention with diet and exercise. As with diabetes, medication use usually indicates inadequate intervention for the patient's deteriorating clinical condition and environmental controls. The hypertension is usually labile and resolves with adequate weight loss. The vasodilating effects of most antihypertensives only add to the amount of accumulating edema, and in some individuals their use delays the onset of the diuresis that occurs with increasing activity and caloric restriction.

Intertrigo

Deep fat folds are prone to **monilial** and bacterial infections with occasional severe ulceration. The physical effort required to cleanse and dry deep fat folds may be beyond the capability of a single caregiver; sometimes two persons are needed to support the **adipose** tissue, while another person performs hygiene. Obviously, this is beyond the capabilities of most families especially if the patient is resisting care; successful treatment and prevention of intertrigo may occasionally require support from a behavior consultant.

Management of severe intertrigo includes daily or twice daily cleansing of non-ulcerated skin using a dilute (1:3 ratio) vinegar and water spray and air-drying with a heat lamp or hairdryer. Clotrimazole or powdered nystatin two or more times per day is also useful. Oral antifungal agents are rarely needed unless the area of involved skin surface area is great or there is ulceration. Severe ulceration responds to very frequent and aggressive nursing care. Diabetes control, as well as improved patient cooperation resulting from behavioral intervention, contributes to successful treatment.

Renal Dysfunction

There is, at present, little evidence of any kidney dysfunction directly related to PWS. **Renal** problems seen in this population have included obstructive uropathy of congenital origin, glomerulonephritis postinfection, "diabetic nephropathy" (i.e., persons with long-standing hyperglycemia and elevated glycohemoglobin levels but without the retinopathy), **renal** tubular acidosis from psychotropic medication (topiramate), and syndrome of inappropriate antidiuretic hormone (SIADH) with **hyponatremia** from psychotropic medications especially oxcarbazepine and carbamazepine (Trileptal and Tegretol), but also from selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics, and valproate, among others.

Patients have developed azotemia that at times is as high as BUN of 70 mg/dl without postural symptoms from the volume depletion of aggressive diuretic use. **Renal** biopsy is rarely attempted possibly due to concerns about both patient cooperation and massive overlying fat. Persons with PWS have a low serum creatinine due to low muscle mass. Creatinine of 0.9 to 1.0 mg/dL should be considered abnormal in this syndrome where typical values are 0.5–0.7 (mg/dL).

Abnormal Pain Awareness and Unpredictable Fever Response

Altered pain sensation and threshold as well as hypothalamic temperature dysregulation have led to underreporting of pain and missed diagnoses of serious conditions that would normally be expected to produce severe pain or fever. Patient histories and direct clinical experiences with inpatients include episodes of acute surgical abdominal conditions, fractures, and serious infections where the diagnosis appears to have been delayed due to the failure of the patient to report pain or to show a fever. Therefore, fever or a refusal to walk must be taken seriously, and a good clinical examination and close follow-up are indicated until serious illness or injury has been ruled out. Patients who show decreased interest in food should be considered potentially seriously ill, medically or psychiatrically. Manipulative or psychosis-related refusal to eat has also been observed but is unusual.

Unreliable Self-Report

Somatic complaints are frequent among individuals with PWS who appear to report numerous symptoms for which objective evidence is lacking. When there is a marked discrepancy between objective findings and subjective stress, discomfort, or functional impairment, malingering should be considered. Although it is no longer considered a psychiatric diagnosis (DSM 5), malingering is "the intentional production of false or grossly exaggerated physical or psychological symptoms motivated by external incentives" (DSM 4). For the individual with PWS,

secondary gain may include obtaining food, medication, and escaping structure in order to procure food or avoiding demands for exercise or other tasks.

Medication Seeking

Medication seeking is prominent with some patients and can result in massive polypharmacy for miscellaneous complaints. These are usually conditions for which objective evidence is difficult to obtain: pain, allergies, reflux disease, constipation, and urinary symptoms. Consequently, adult patients are frequently on an excessive number of prescription and over-the-counter medications and topical preparations. Persons with PWS are often very attached to their medication regimens and will sometimes vigorously resist change. They sometimes request liquid medications that are sweet to the taste. Prescriptions for symptomatic relief should therefore always be time and dose limited and the benefits verified by a caregiver. Validity is verified if symptoms interfere with the person's level of function. Patients with PWS should not have unsupervised visits to a physician. *Persons with the disorder cannot be allowed to dose themselves with "as needed" medications.* Non-drug therapies are preferred: heat, cold, massage, sympathy, or reassurance.

Abnormal Temperature Regulation

Frank **hypothermia** occurs in PWS persons. In two well-studied patients, hypothermia was heralded by a change in behavior followed by decreasing activity proceeding to near coma. They did not want to eat, did not complain of being cold, felt cool to the touch, and became ashen. Hypothermia (81°–94 °F), decreased blood pressure, bradycardia, and slow respirations were observed. Laboratory studies revealed decreased hemoglobin, low WBC, decreased platelets, **hyponatremia** without acidosis or **hyperkalemia**, and elevated **renal** and liver function tests. All of these changes returned to normal levels over several days as the patients were rewarmed. Sepsis was suspected but blood cultures were negative [37]. Neuroleptics have clearly played a contributory role in the development of hypothermia, and discontinuation is associated with improvement [38]. Hypothermia has usually occurred when the outside temperature was cool. Susceptible patients have had repeated episodes during the winter and experienced relief during the summer months. Bray et al. (1983) have made similar observations [39].

Hypersomnia: Daytime Sleepiness

Abnormalities in the sleep of persons with PWS have been documented at all ages with and without obesity [40]. Excessive daytime sleepiness appears to be a characteristic of PWS, but excessive medication and obesity hypoventilation must be ruled out as contributing to the symptom [41]. Some patients meet criteria for narcolepsy and benefit from appropriate medications [42]. Stimulant medications and modafinil have been useful, keeping in mind the risk of mood activation in susceptible patients. It is certain that some patients use their capacity for short sleep latency as an escape-avoidance mechanism and can respond to behavioral incentives to stay awake in the classroom or day program as well as a dense schedule of activities.

Skin Picking

The "skin picking" behavior of PWS has a wide range of severities from patient to patient and sometimes in the same patient over time. A stability over time is more typical, however [43, 44]. Some patients have occasional minor skin picking while others maintain large open wounds [45].

Here, skin picking is defined as an activity that goes on when the patient is calm and does not appear to be expressing emotional distress by the behavior. It has been related to boredom and anxiety, but objective evidence for this is difficult to establish. No specific intervention has been uni-

formly effective, although N-acetyl cysteine [46] and low-dose topiramate [47] have demonstrated some efficacy as reviewed by Bonnot [48]. And, anecdotally, prevention strategies such as insect repellent to decrease bug bites have been helpful. The behavior often extinguishes if healing of the wound is achieved. There has been some success using protective dressings, even a scuba suit or pantyhose, for severe injury and intractable picking. An intense sensory program and a dense schedule of alternative activity until wound healing occurs have been effective in our experience. Severe disfigurement, recurrent infection, and anemia are reasons to consider hospitalization for this problem.

Because skin picking behavior occurs intermittently and clandestinely, behavioral interventions targeted at the activity itself are difficult to implement. Some parents have reported success by attaching a major reward to the ***healing*** of a lesion. Daily photographs of the healing could motivate but could also discourage the patient. This approach is compatible with the basic principle that any attention to the issue should be matter-of-fact such as requiring the patient to observe social conventions and good hygiene. Patients may cease the behavior spontaneously or to obtain a reward; they may also substitute another area of skin to pick. In some cases, frequent picking behavior interferes with the patient's other activities.

Rectal Self-Injury

Rectal self-injury is a problematic behavior occurring in some persons with Prader-Willi syndrome and can produce unexplained medical symptoms which sometimes leads to unnecessary medical tests or treatments when the behavior is not known to the physician [49]. The behavior is common in PWS and not well understood. Fortunately, it becomes serious in only a small number of persons with PWS. This includes patients with frequent rectal digging/injury that results in medical problems such as bleeding, fissures, infection, or fecal incontinence [50].

Indirect evidence of the behavior can aid in the diagnosis of unexplained medical symptoms even if the behavior has never been directly observed.

- Excessive time spent in the bathroom (a PWS trait without rectal picking).
- Feces or bloody smears on hands, toilet, fixtures, shower, bathtub, or bed linens.
- Bowel incontinence, urgency, or diarrhea (due to reflex bowel emptying following rectal stimulation).
- Anemia from chronic blood loss, while rare, can be severe. Acute hemorrhage or perforation has not been reported.
- Chronic ulceration is well documented by endoscopy and has been misdiagnosed and treated as inflammatory bowel disease (IBD) [49].

Based on extensive experience, the following should help clinicians to avoid some common misunderstandings about the behavior.

- The behavior is often misunderstood as "obsessional"; however, medications targeting OCD have not been helpful.
- Rectal picking/digging does not appear to be a sexual behavior, nor is it a symptom of hypersexuality associated with mania. Clinical experience does not support any correlation with sexual abuse, nor is it intrinsically a psychotic behavior [i.e., a symptom indicating psychosis], but it has been observed to increase in the presence of psychosis or mood instability and can sometimes be traced to the introduction of mood elevating medications such as SSRIs [51].
- Rectal picking/digging appears to be a nonspecific stress symptom. Marked increases in the behavior have been observed in association with ongoing interpersonal conflict, punitive disciplinary approaches, as well as during episodes of psychosis and mood instability. Diminution and/or elimination of the behavior has occurred when the underlying illness or stressor is addressed effectively.

- The behavior is certainly related to unmet sensory needs, and intense sensory programs have been dramatically helpful [52] when implemented with consistency. Generally, adults who benefit from sensory programming will continue to need the intervention as their sensory needs do not change.

Dangers and Challenges of Hospitalization of a Person with PWS

Medical crisis intervention for persons with PWS may require hospitalization. This exposes the patient to a large number of professionals who are unfamiliar with PWS.

Regardless of the medical issue, hospitalizing a person of any age who has PWS requires a willingness to expect the unexpected. The following are General Guidelines for Hospitalization of a Person with PWS:

- Unless the patient is in a rehabilitation facility, a common result of hospitalization for medical illness is inactivity; this puts the patient with PWS and obesity at greater risk. Physical therapy consultation is appropriate upon admission.
- Regardless of IQ, regardless of how articulate the patient is, hospital personnel need to be aware that the person with PWS will not exercise good judgment which is a potential danger to the implementation of his own care.
- Regardless of IQ, do not expect him to understand as well as he talks. He *will* have subtle processing problems with receptive language and will *easily* misunderstand what is said to him.
- Do not discuss his care and possible outcomes or uncertainties in his presence. *Rather, speak to the guardian privately about all matters of substance*. Leave communications to the patient about substantive matters to the guardian/experienced caregiver who will have a better sense of how much information to give and how much uncertainty the patient can tolerate.
- Use your interactions with the patient to assess his mental status, comfort level, anxiety, etc., not to impart information. Medical personnel should discuss pets, sports, and special interests or use other pleasantries to establish rapport and to help make him feel included.
- Full guardianship of the adult with PWS is the ideal. If the patient is his own guardian, release forms for communications can be utilized as needed, and, if these are not agreeable to the patient, an emergency court order may be required to avoid an untimely legal crisis while in the hospital. If the patient is permitted to participate, unfiltered, in discussions about medical decision-making, there is a high probability of precipitating a crisis of suboptimal care. Informed consent must be modified as with a child.
- Utilize the years of experience of the parent or caregiver when interpreting physical signs, symptoms, complaints, or behavior. Failure to do this is the most frequent error made by medical personnel when caring for a person with PWS. If the parent is concerned about a symptom, the clinician should be concerned.
- With respect to food, without a low-calorie diet plan, the patient will consume more food than needed and will gain weight.
- Good management is preventative. He or she requires constant supervision. This prevents anxiety that leads to disruptive behavior. Also, it prevents food foraging that also creates anxiety, etc.
- Choking is a common cause of death and sometimes takes place when food is obtained surreptitiously and then gorged to escape detection [53].
- A designated member of the nursing team for each shift must, in consultation with the parent/guardian, approve all edibles that enter the room or otherwise reach the patient. Errors in the dietary department are commonplace since the recommended diet is so unusual.
- Place a sign on the door instructing all personnel, including dietary staff, not to provide any

food or beverages directly to the patient, including regular meals.

- If the patient has a healthy weight, prescribe the diet that most closely resembles what he is receiving at home; if he is overweight, 800 calories/day is generous and may need to be modified.
- Weigh daily. Weight gain in a hospital setting can be breathtakingly rapid if the patient is ambulatory and accessing food and less dramatic but inevitable if he is receiving a "normal" diet.
- Weight loss in a hospital setting can be very rapid if the OHS patient is required to be active and is undergoing a spontaneous diuresis of retained fluid. This does not mean that he is being underfed.
- Behavioral problems are nearly always attributable to anxiety or disappointment. Expect him to be anxious and to benefit from known structure or schedule, general reassurances, and distractions in addition to one-to-one supervision/companionship.
- The patient will likely be anxious just by virtue of being out of his own routine. Anxiety in PWS can result in unexpected, even outrageous behavior and occasionally a transitory psychosis. On all medical/surgical units, and on most psychiatric units, *the patient with PWS requires a family member, familiar caregiver, or familiar group home staff to stay with him at all times*. If this is not available, the hospital must cover the gaps in 1:1 coverage. This will reduce anxiety and therefore minimize the risk of disruptive behavioral problems interfering with care.
- These behaviors stem from uncertainty, anxiety, misunderstandings, and disappointments and are largely avoidable if good management is provided. Agitation may be associated with aggression but usually is not. Staff need to be prepared for this and approach it like the disruptive behaviors of a neurologically confused person and avoid blame. It is part of the syndrome.
- Sedation for agitation is contraindicated especially in the presence of OHS or any cardiopulmonary compromise and is unlikely to be useful in any case. Skillful verbal or nonverbal de-escalation is indicated and works about as quickly.
- He may not tolerate indwelling catheters, lines, or IVs and is very likely to pull them out if unsupervised or agitated.
- Avoid tracheotomy and tracheostomies. Repeated experience is that these situations deteriorate, and virtually all patients in our experience have pulled out their own tracheostomy tube or stuffed foreign bodies into the tube or tracheostomy stoma. The breathing disorder in the extremely obese is generally hypoventilation and not primarily obstructive.
- Do not expect the patient to be reasonable, especially if he is displaying any degree of negative emotion. If he is uncooperative, he will not necessarily be responsive to explanations or threats of negative consequences. Once he becomes visibly agitated, it is likely that he is not processing anything being said to him. It is usually best to just stop talking.
- People with PWS are well known for providing misinformation of all types, even without intent or secondary gain. Do not expect him to be a reliable reporter; do expect him to unintentionally misinform, use words incorrectly, confabulate, and manipulate, all without obvious confusion, opportunity for gain, or other motivation. On the other hand, he may be speaking quite accurately and needs to be listened to. Your initial response should be serious in tone and noncommittal in substance. On important issues such as medical symptoms or history, listen seriously but *always* verify with the caregiver.
- Do not do the full ROS (review of systems) with the patient. People with PWS are highly suggestible, and it is better not to give them new ideas of symptoms to report. It helps to substitute general open-ended questions such as, "Is anything hurting or bothering you?" with follow-up questions as needed. Interference with level of function and enjoyment of preferred activities are the best indicators of a physical ailment.

- Expect him to underreport pain, especially visceral pain. Take complaints of pain seriously even if he does not appear to be in pain.
- Do not rely on the absence of signs of nausea, vomiting, fever, or pain to assess abdominal health or recovery of gastrointestinal function after anesthesia. Loss of interest in food is a serious sign and may come late in the course of an acute abdomen. Familiarize your clinical team with the signs of gastroparesis in PWS [54, 55].
- While sedation may be needed to complete diagnostic or medical procedures, it is extremely risky in the obese patient whose airway is difficult to manage in the best of circumstances. Weigh benefits to risks, and substitute an honest discussion with the guardian rather than practicing "defensive medicine."
- The Clinical Advisory Board of the Prader-Willi Syndrome Association (PWSA-USA) can be accessed through (800) 926-4797 and responds to international as well as domestic requests. Please use this support; there is no shame to ask for help when dealing with an unfamiliar and complex disorder.

Conclusion

Prader-Willi syndrome presents challenges to medical personnel because of the extreme complexity of the disorder combined with limited opportunities for physicians, nurses, therapists, and others to gain clinical experience. **Humility** is part of the necessary clinical skill set.

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18 Social Work Interventions: Advocacy and Support for Families with Prader-Willi Syndrome

Barbara Y. Whitman and Lisa A. Graziano

In Time of Need: Resource and Advocate

The psychosocial impact of Prader-Willi syndrome (PWS) affects the entire family as well as schools, community, and society. For the family, from the moment of the birth and diagnosis, the added stress usually disrupts the established functional balance, at least temporarily. In addition, any personal, family, or environmental difficulties present *before* the birth of the affected child may make it harder to reestablish and maintain adequate family functioning and meet the infant's special needs. For most families, this initial stressful period—full of grief, confusion, and often overwhelming challenges—is just the beginning of a journey through a lifelong maze of unique experiences, educational challenges and needs, and behavioral differences and uncertainties. These unique, special needs of individuals with PWS are not always fully appreciated outside the family and sometimes not even by the extended family. As a result, many families face a complex, multilayered service system that often may seem designed more to deny than to deliver services. Too many families continue to report that professionals and service systems fail to recognize the physiologic etiology and unyielding nature of the food-related and other neurologically related constellation of behaviors, often implicitly if not explicitly citing poor parenting or purposeful bad behavior as the source of difficulty. In the face of this interpretation, the process of obtaining appropriate services can become adversarial, with parents often feeling alone, isolated, and exhausted. Indeed, in a study of stress and social support in families of children with PWS, Hodapp et al. [1] found that parents of children with Prader-Willi syndrome reported higher levels of parent and family problems, suffered greater pessimism, yet got less support from professionals when compared with parents of similarly aged children with cognitive deficits from other causes. This was despite a major thrust in the decade prior to the study for "family-focused" and "family-driven" intervention strategies. Unfortunately, despite our increased knowledge of the syndrome and its impact on families, it appears that many of the same issues

The authors recognize that other professionals such as licensed counselors and psychologists may serve the role and function described in this chapter. However, the roles and functions described in this chapter have traditionally been assumed by social workers starting from the medical social worker in the NICU or hospital unit caring for the newborn.

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still exist [2]. Targeted social service intervention by the social worker can (1) help the family reestablish a working balance, while (2) providing education and guidance, and (3) providing support to obtain and coordinate multiple medical and early intervention services for the affected child. Further, as a member of an interdisciplinary team, the social worker identifies the frustrations, demands, and conflicts encountered by families and functions as an advocate for both the family and the team.

Initial Sources of Stress for Parents: Birth With rare exception, families begin interacting with multiple service-providing systems from the moment of birth. Immediately after birth, hypotonia and accompanying feeding difficulties signal the presence of some underlying medical problem that often necessitates extended hospital stays in special care nurseries accompanied by multiple and painful diagnostic testing including testing for PWS. In addition, frequently the baby is transported to a specialty pediatric facility that may be quite distant both from the delivery hospital, where the mother may remain for a while, and from the family home. Distance, parental health, and even travel expenses or transportation difficulties may prevent parents from being with their infant at this time, further increasing stress and anxiety. Moreover, parents may encounter, and be overwhelmed by, multiple medical specialists, noisy and unfamiliar biomedical equipment, constantly changing staff, and confusing communication processes. Typically, the newborn infant's greatest challenge immediately after birth is feeding, presenting the social worker the first opportunity to provide information and support to the family [3]. Most newborns with PWS lack sufficient muscle tone and motor coordination necessary to breastfeed or even bottle feed. As soon as feeding difficulties are detected, the newborn is usually transferred to a neonatal unit where alternate feeding strategies are initiated, including the use of special nipples and the placement of a nasogastric tube. When the PWS diagnosis is confirmed, many physicians immediately prepare for the placement of a gastric feeding tube, erroneously believing that G-tube placement is always necessary. The social worker can support the family by providing the NICU team and the family with state-of-the-art information obtained from PWSA | USA about the pros and cons of G-tube placement in infants with PWS and the potential for early growth hormone medication to alleviate feeding challenges.

During this time, the stress of radically altered, unfamiliar, and unpredictable circumstances, combined with extraordinary levels of anxiety, change the dynamics and processes within the family unit, which, without support and intervention, may foreshadow a shift into a less functional system. Proper healthcare for the infant dictates provision of support and care for the parents during this time, along with a life-care plan based on an accurate assessment of family stresses, family processes and dynamics, finances, coping mechanisms, extended family and community resources, and the ability to make future plans. The social worker is the logical choice as a communication liaison for the care team, an emotional support for the family, and an investigator of the needed facts for developing a long-term care plan for both the child and family.

Reactions to Diagnosis Full genetic confirmation of Prader-Willi syndrome has only been available since approximately the year 2000. Prior to that time, the diagnosis of PWS may have been suspected; however, depending on the underlying genetic mechanism, an official diagnosis may have been delayed until the emergence of hyperphagia and the accompanying obesity. Prior to any confirmatory genetic tests, the average age at diagnosis for those with a deletion was 6 years and for those with uniparental disomy, 9 years [4]. Many families who experienced such a diagnostic process reported that "having a name for it" was an enormous relief. In addition to having some framework for knowing what to expect, many parents said that finally having a diagnosis relieved an often-unspoken fear and guilt that they had somehow caused or were causing the problem. At the same time, many reported experiencing an active grief process as they realized the unreality of another, often unspoken hope that eventually the problem would be named *and fixed.*

By contrast, today when the profound hypotonia of affected newborns signals a genetic workup, it is often followed by a confirmed diagnosis while the infant is still in the special care nursery. Thus many families now must concurrently absorb and comprehend that their newborn "isn't quite normal" *and* the implications of PWS. With rare exception, parents experience an acute stress associated with learning of the genetic abnormality. Each parent may silently wonder if they were somehow to blame; conversely, they may each, often unconsciously, blame the other. Whether the etiology is a deletion or uniparental disomy, parents need to be regularly assured that there is nothing they did to cause the disorder nor anything they could have done to prevent the disorder. Mother and father each explicitly needs to hear that *nothing* each did (or didn't do), drank (or didn't drink), medications or illegal drugs each took (or didn't), nor any activities and exercises the mother engaged in (or didn't) prior to conception or during pregnancy was causative.

Research indicates that, faced with extraordinary and overwhelming stress (earthquake, fire, accident, birth of a child with disability), people respond in one of three predictable ways [5, 6]. Approximately 15% of the people can and do take positive action, 15% are emotionally paralyzed and unable to act, and 70% exhibit odd behavior. Even beginning the adjustment to a diagnosis can take 9–12 months. Family members often experience the classic stages of grief, moving in and out and between feelings of (1) shock and numbness, (2) yearning and searching, (3) disorientation and disorganization, and (4) resolution, reorganization, and integration. But these stages are not accomplished in a vacuum nor do parents have the luxury of coming to terms with their feelings before they must provide day-to-day care for their child, make decisions, and seek services. Parents may take their baby home feeling anxious and unprepared to handle the special feeding techniques. Infants with PWS have a weak cry and little energy for crying, so a parent may be trying to provide for the infant's needs in the absence of normal infant cues signaling hunger, distress, and discomfort. They may immediately face the need for understanding what early intervention services are required, how they are obtained, and finding the financial resources for the services. Further, participating in multiple services can be time-consuming. If a family was planning on, or needs, two incomes, lifestyle adjustments may be needed. If the family already has other children, their needs cannot be put on hold. Previously unresolved conflicts regarding child rearing and discipline will be exacerbated and magnified under the stress, potentially to the detriment of the family and marriage. Restrictions imposed by the syndrome often cause other family members to feel trapped and helpless, and emotional ties become distorted. Without adequate support through this period, the level of reorganization may be fragile and insufficient to adequately meet the challenges facing the child and the family.

It is important at this point for the social worker to fully assess, monitor, and, when necessary, intercede in family interaction patterns so that, over time, the resources and capacity of family members are not overtaxed to the point that parents doubt their capacity to fulfill their prescribed roles. If the previously developed habilitation and management plan provides inadequate support, the social worker must act as advocate for the family with the team, reconvening the necessary professionals to design a more comprehensive habilitation plan. At the same time, the social worker must establish and maintain an ongoing supportive relationship with the family so that he/she can act as a link to the team and community resources. In this role, he/she may review, reinforce, and, where necessary, clarify team recommendations to the family and work to establish the necessary linkages in the community for obtaining needed services. Although some families reach grief resolution, several authors describe the chronic sorrow or grief that typically occurs as families address this lifelong disorder and its consequences [7].

Advocacy for Early Intervention Treatments and Services The social worker's next opportunity to support the family typically occurs when the newborn is released from the hospital when

the social worker can be particularly helpful in identifying and connecting parents with the appropriate federal, state, and local support and intervention programs and services. Among those, perhaps first and foremost, parents and extended family members should be encouraged to contact the national PWSA | USA and their state's PWS affiliate or chapter as soon as the diagnosis is made in order to receive personal support, accurate information, and guidance for medical and therapeutic treatments and interventions. The social worker will likewise benefit from maintaining good working relationships with staff at the national, state, and local PWS organizations.

Newborns and infants with PWS typically benefit from a feeding specialist and/or oral-motor therapy delivered by a speech and language pathologist. Occupational or physical therapy should begin as early as possible and continue at least through toddlerhood. Speech and language therapy can begin as young as 1 year old and generally continue well past toddlerhood. Sensory integration deficits, commonly caused by low muscle tone, should be addressed by a physical or occupational therapist who has special training in sensory integration therapy.

Federal law mandates that all US children who are determined to be at-risk for developmental delay shall be eligible for early intervention services from birth until the age of 3 years (Part C of IDEA) [8]. These early intervention services are designed to help the young child with delayed and atypical physical, cognitive, communication, adaptive, and social or emotional development. IDEA further mandates that early intervention services must be provided by qualified personnel, in natural environments, and at no cost to families except where states provide for a system of payment, such as sliding scale. Services are overseen by each state's office of developmental disabilities and are delivered by a designated agency or by the local school district. By definition, all children diagnosed with PWS are eligible for early intervention services. The social worker can support the family by providing them with the contact information of the early intervention program and encouraging them to make contact as soon as possible to expedite the provision of services.

Other services that can be delivered by the early intervention program include nutritional services, advocacy for school supports, behavioral education and supports, and respite services for parents. The social worker is encouraged to continue support of the family by anticipating the challenges that are typical during each phase of the syndrome and at various stages of the child and family's development to help the family remain proactive and empowered.

In addition, many parents find it helpful to connect with other parents. This can be done formally through the PWSA | USA's parent mentoring program and age-based Internet support groups and through one of the PWS state or local support groups. It is often recommended that parents avoid searching the Internet for prognostic-ative information about PWS until they are through some of the more vulnerable periods of grief and are more able to cognitively evaluate the validity of the information.

Moving Forward As the intensity of the initial reactions lessens, parents can more purposefully focus on integrating this child's special needs into the daily fabric of family life. Early in their educational process, many parents will request as much information about the syndrome as possible, attempting to reach and absorb some understanding about PWS. Others simply want to know "what to do next," perhaps acknowledging at some preconscious level that true understanding is illusive. There are inherent emotional traps in each request to which the social worker must remain alert. For the family requesting as much information as possible, the social worker needs to monitor the emotional impact of the information. The information presented must be factually and sensitively presented. However, despite the request for information, for some families the trauma of learning about PWS may distort their ability to listen and absorb facts, creating a backlash of anger directed at what they perceive as insensitivity in the presentation of the facts. Questions such as, "Are you telling me that my

child won't be able to go to the same school that my other children have gone to? It's the same one I went to," indicate that the impact of this disorder in this family may reach into many sacred, well-loved areas whose constancy over time has always offered the family a sense of safety and stability. Thus, a tempered, yet realistic answer should be provided, indicating that we cannot yet predict the severity of this child's learning deficits, nor do we know how easily, and extensively necessary modifications will be provided by the school. Further, it can be indicated that research is ongoing regarding the management of some of the more difficult areas of the syndrome, so that by the time this child reaches school age, school placement issues may be quite different from those currently encountered and may or may not preclude attendance at any particular school.

By the same token, those who request, "Just tell me what to do next," may be realistically relating that they wish to act appropriately based on what is now needed and will seek further guidance as the situation changes—a perfectly valid coping strategy. The team, however, must be alert for the family that is so overwhelmed that they need further supports and for the family that picks and chooses what is comfortable to hear, acting on what is convenient. In all instances, it is recommended that written information and video or Internet links be available to be taken home and reviewed.

Now let us look at the larger family system and some of the specific stressors PWS imposes upon it.

Long-Term Family Concerns

Family Systems Are Clearly Unique: What Is a Family? While many currently frame this question as a political, moral, and ultimately a legal issue, the question is raised here in order to define the "family unit" for purposes of support and intervention. Conceptually, a family is defined as a small social unit of interconnected persons that reciprocally influence one another over time [9]. However, family systems are distinct from other social units based on two unique properties. First, unlike other social units such as work, task, or interest-focused groups, *families are formed based on reciprocal emotional ties*. While legal contracts—such as marriage—may be struck because of these emotional ties, the primary glue that binds a family is affectional; the emotional bonds of attachment, loyalty, and positive regard are paramount. Secondly, *family membership is virtually permanent.* Other social groups have recognized means for joining and leaving; resignation or being fired from a family is virtually impossible. For many, that permanency is a source of support, a foundation for growth, and a recognition that, no matter what, the family will always be there. For others, it is an imprisoning, stultifying entrapment that suppresses growth and from which there is no escape. Whatever the feeling, the ties are permanent. Parents may divorce, but the emotional ties, whether positive or negative, inextricably bind that child to both parents in perpetuity.

Studies document that *family "processes"*—or how, and with what emotional tone, a family interacts—have greater impact on a child's developmental outcomes than does family composition. From the viewpoint of family processes as primarily determinative, this definition is neutral on the political/moral issues of *family composition*, recognizing viable family structures beyond the traditional two-parent family including single parent families, extended family caretakers, and single sex couples raising children.

When a family member has PWS, understanding family processes, and the impact of PWS on these processes, is key to management [10]. Yet, despite its importance, research in this area is virtually nonexistent. Thus we turn to collective clinical wisdom from families served, data and experience from the national Prader-Willi Syndrome Association | USA, and general research findings regarding families and developmental disabilities. The purpose is to provide parents, grandparents, and those multidisciplinary teams who would work with these families a basis for understanding the many complex, and often contradictory, feelings reported by

families and to provide some examples of the multitude of creative coping strategies developed by these families.

Marital Relationship The stressors of everyday life can greatly affect both general family functioning and specifically the ability of the family to adequately provide for their child with PWS. Within the family, *the marital relationship* is particularly vulnerable to stress, even those relationships of longer duration. Frequently, marriages are in their early stages, and spouses are learning how to rely on each other when their children are born. Medical appointments, in-home therapies that can feel "intrusive," harried schedules, the ongoing needs of other children or extended family members, work overload, financial challenges, and other "external" precipitants of stress may be so overwhelming that they increase the need for social work intervention. Already existing areas of difficulty and unresolved conflicts will be exacerbated at this time. Further, it is not unusual for each spouse to be at a different stage of absorbing and adjusting to the presence and implications of PWS for their child and for their family. As a result, each spouse may be unable to respond to the emotional needs of the other. Early on, special feeding demands may limit access to qualified babysitters, so there is little or no time for private couple interactions. As the child gets older, potential behavior problems may continue limiting childcare options. The needs of other children add to these concerns. Both spouses may feel confused, angry, and trapped. Sometimes, the depth of frustration and level of unhappiness do not emerge for some time. As a result, expressions of feelings toward their child and each other may be blunted or erratic, unpredictable, and even episodically volatile. Van Lieshout et al. compared the impact of family stress on the marriage and on behavior of spouses toward the affected child in parents of children in three syndrome groups: Prader-Willi syndrome, fragile X syndrome, and Williams syndrome. In all groups, higher perceived family stress was related to more marital conflict and less parental consistency. However, parents of children with Prader-Willi syndrome more often expressed this stress as anger directed toward the child. This child-directed anger was not without consequence; in those families evidencing the highest parent anger toward the child, the child was noted to have a more negative personality and poor behavior when compared with those from families in which parental anger was less. These findings extend the earlier findings of Holmes and associates and Whitman, who demonstrated that if intervention is not carried out immediately after diagnosis and again whenever problems arise, behavior problems are more likely to develop or compound. A high level of family conflict acts as a predictor of behavior problems, reinforcing the need for social work intervention.

In addition, for most families, financial concerns will continue throughout the child's lifetime. Worries about payment of medical bills and the cost of other services (e.g., respite) can become overwhelming. To the extent that the marital relationship is strained, the energy each spouse expends on coping with those strains drains the energy available for dealing with their child(ren), and as the research by an Lieshout [7] indicates, in those families coping with Prader-Willi syndrome may be manifested by greater anger directed toward the affected child. Thus, the social worker should continually assess the status of the marital relationship, obtaining the appropriate interventions as needed. This may be as simple as finding funding and trained respite providers to allow the couple some time alone or as intense as providing couples therapy.

Parenting Issues Many families are able to maintain a stable marital relationship, but fundamental differences in parenting styles create a constant source of conflict. While there are many "right ways" to parent, the extraordinary need for sameness and consistency required by children and adults with PWS demand that parenting style differences be identified early and sensitively addressed to prevent later intractable behavior problems. Nutritional management remains a primary issue for affected individuals. How well food is managed has critical implications for all

other areas of behavior management, yet it remains an area that parents often find difficult to discuss. Even when parents are in perfect accord over the need for dietary vigilance, particularly at home, they may be at odds over how to handle food-related behavioral incidents in public. Thus, while one parent may respond to an impending incident over a denied treat by preparing to leave a restaurant, the other may advocate giving in "just this once" in order "to avoid an incident here." Such differences are quickly apparent to the affected child, who soon learns to manage his/her environment through bad behavior. Mutually acceptable methods for handling these differences need to be developed as soon as the differences arise. If the couple is unable to come to some decision rules on their own, counseling help should be sought [11, 12].

Parents may also be in conflict about the division of labor regarding nutritional and behavioral management, with one parent feeling burdened with too much responsibility while perceiving that the other is insufficiently so. Thus, if a child gains excess weight, one spouse often attacks the parenting style of the other, diverting attention from solving the problem of how to prevent further weight gain. Leaving such issues unresolved leads to families becoming dysfunctional, if they are not already so.

Even when there are no differences between parents regarding nutritional management, defensiveness is a natural first response when a child gains excess weight. Many families worry that the professional staff with whom they work will perceive them as "bad parents." Many express guilt that in "stealing a few moments for themselves," they failed to lock a food storage area and found their child "indulging" vigorously. Over time, many families have developed a number of ways to cope with weight and behavior control issues. A survey of 293 parents/guardians of children with PWS aged 25 years and younger identified a number of strategies for coping with food and eating behaviors and a second set of strategies for controlling access to food, as well as the strengths and weaknesses of each [13]. The most consistently effective are listed in Table 18.1, while those that are often effective (given the right conditions) are listed in Table 18.2. The effectiveness of many strategies depended on family characteristics. For example, many respondents indicated that lack of effectiveness was related to (1) the time, energy, and stress involved in maintaining a strictly regimented diet; (2) other caregivers (such as school personnel) not understanding the importance of dietary restrictions and how to implement them; (3) difficulty making appropriate food choices at restaurants and parties; (4) difficulty limiting

Table 18.1 Effective strategies for nutritional management

Strategy	Respondents[a] (*N*)	Effectiveness score[b] (Mean ± SD)
Lock away food	116	4.5 ± 0.9
Always supervise the child, particularly around food	143	4.2 ± 0.9
Keep lots of low-energy foods on hand for snacks	125	4.2 ± 1.0
Keep lots of low-fat foods on hand for snacks	120	4.2 ± 1.0
Count kilocalories and have less energy at a meal to allow a snack later	104	4.1 ± 1.1
Try to provide more nonfood-related rewards and treats	124	4.1 ± 1.1
Give the child small portions	141	4.0 ± 1.0
Give other children treats when the child with Prader-Willi syndrome is not around	101	4.0 ± 1.1
Only have snacks when the child with Prader-Willi syndrome is not around	105	4.0 ± 1.1
A special diet	85	4.0 ± 1.1

[a]Not all respondents rated every strategy; a total of 154 families provided ratings

[b]Strategies were rated on a scale from 1 to 5, with 1 being least effective and 5 being most effective

SD standard deviation

Source: Goldberg et al. [13]

Table 18.2 Moderately effective strategies for nutritional management

Strategy	Respondents[a] (N)	Effectiveness Score[b] (Mean + SD)
Keep snack food in your bedroom or other special locked area	94	3.9 ± 1.2
Only serve food from the kitchen, not from the table	86	3.9 ± 1.2
Send special snacks to school	114	3.8 ± 1.2
Give the child half a portion, and let the child ask for seconds	109	3.8 ± 1.2
Keep strict mealtimes	91	3.8 ± 1.3
Everyone eats only low-fat and low-energy foods	76	3.6 ± 1.2
Put food on smaller plates so that it looks like more	97	3.6 ± 1.2
Discuss the menu before going to a restaurant	106	3.6 ± 1.3
Keep limited amount of food in the house	69	3.6 ± 1.4
Meet with caregivers and teachers to explain the syndrome	141	3.5 ± 1.2
Allow the child to be part of menu planning and preparation, making him or her aware of energy and fat content	103	3.5 ± 1.2

[a]Not all respondents rated every strategy; a total of 154 families provided ratings
[b]Strategies were rated on a scale from 1 to 5, with 1 being least effective and 5 being most effective
SD standard deviation
Data source: Goldberg et al. [13]

access to food (a difficulty that increased as the child got older); (5) the impact of limiting access on the other children and general family life; (6) a busy lifestyle; and (7) general difficulties in managing behavior problems. A number of respondents highlighted the need for unwavering consistency of approach both between parents and across time. Thus, while the particular strategy that is effective may differ between families, the need for consistency is vital for all families.

Siblings With rare exception, perhaps no area of research is more neglected than the impact on siblings living in a family coping with PWS. When parents are obliged to constantly focus on the needs of the affected child, the risk for siblings having adjustment difficulties, although not inevitable, is clearly increased [14]. Anecdotal evidence suggests that siblings of a child with Prader-Willi syndrome often have conflicting and confusing feelings about their brother or sister. They may be embarrassed by their sibling's odd or unusual behaviors, including temper outbursts, autistic-like behaviors, and the family's need to use locks to restrict all access to food. The constant risk of behavior problems in public, particularly around food-related issues, is often a chronic source of stress and anxiety, frequently leading to a "Does he/she have to go?" query. Siblings often express reluctance to invite friends to their home while at the same time indicating a lot of guilt associated with this reluctance. Resentment is frequently voiced by siblings when they perceive parents holding them to a higher standard of conduct than their sibling with PWS. Jealousy at the attention given the affected child is often noted, along with a conflicting feeling of being glad they can "hide" and "get away" with doing what they want while the family is preoccupied with the affected sibling. Often siblings are pressured into parenting roles (e.g., "I have to run to the store; make sure he/she doesn't get into the pantry while I'm gone"), given additional responsibilities, or forced to "grow up" too quickly. Even feelings of guilt that the sibling does not have food restrictions often emerge.

It is important to give siblings permission to express all feelings regarding their brother or sister and the syndrome. Parents may need to be taught how to encourage this expression, and how to hear them in a nonjudgmental way. Parents can model for their children by inviting them to medical or counseling appointments where the parents identify and talk about their own feelings. Attending siblings should be encouraged to ask questions; the tone of their questions can serve as a conduit for asking, "That

makes me wonder if you are feeling …," and pave the way for the siblings to air concerns and feelings.

Younger siblings may wonder if they can "catch" Prader-Willi syndrome, while older siblings may worry about having a child of their own with PWS. Most geneticists encourage genetic counseling for the maturing adolescent so that all questions can be honestly and sensitively answered.

Many adult siblings retrospectively report that they knew their family was different and had to be more careful about food, but they didn't see it as "abnormal." Research documents that many adult siblings feel they have developed a greater understanding and acceptance of differences and a sense of empathy for those who are disenfranchised.

The Extended Family Many families have extended family members from whom they usually get support. Grandparents, parents' adult siblings, aunts, uncles, and even cousins often can be called on for childcare, emotional support, and occasionally financial relief. The extended family can also, unintentionally, become an additional source of stress. Many grandparents have stated, "You can keep him on a diet at home, but at my house it's my grandparent's right to give him what he wants!" In family systems that regularly or primarily socialize with and draw support from each other, a family meeting of all concerned should be convened as soon as possible after the diagnosis has been made. The purpose of this meeting is to ensure that all members have the same information and are provided the opportunity to ask questions and to seek understanding [15]. Concerns about a recurrence risk in their own families can be addressed. The importance of controlling access to food, limiting intake, and establishing consistent behavioral approaches across environments must be underscored since one of the most common stressors voiced by parents is that extended family members do not follow their directives regarding food and overall care, thereby exacerbating the child's weight and behavioral symptoms. The special pain of grandparents, both for their adult child who is the parent and their grandchild, can be aired and supported. Periodically, the social worker will need to inquire how these relationships are functioning and whether additional meetings are necessary.

Additional Major Concerns

Over time, the relationship of the social worker with the family is such that multiple additional concerns may be raised and addressed. Among these are behavior management, community resources, education, guardianship, and adult living and working arrangements. Since these areas are addressed at length elsewhere in this volume, they will be dealt with only briefly here.

Behavior In addition to nutritional management, behavior is the other major challenge for families, and one that increases as the affected individual gets older. Although variable, the average age at which typical PWS maladaptive behaviors begin is 2.5–3 years, about the same time as the hyperphagia food drive begins. Behaviors typically include increased rigidity and oppositional reactions, tantrumming, increased need for sameness, obsessive-compulsive like behaviors, and skin picking. It is important to identify and intervene in areas of concern as soon as they arise and before a self-reinforcing pattern is established. While consistency is the hallmark of behavior management, it must be remembered that the constant food vigilance and behavior management needs of the child with PWS can drain family emotional and financial resources. Families are often unable or reluctant to admit their exhaustion; it may, however, become evident in clinic visits when a family fails to address or intervene in their child's disruptive or inappropriate behavior. Clinic staff may misinterpret this lack of response as chronic inadequate parenting and may respond to the family in ways that prevent a full understanding of the level of exhaustion. In addition, acting out and tantrums make families reluctant to go out in

public or invite others to their home, encouraging isolation. The social worker needs to be alert to and acknowledge this exhaustion. Realistic recommendations for behavior management and additional family support may temporarily be needed to allow the family to regain sufficient stability to deal adequately with the behavior difficulties.

Community Resources The family's need for community services will vary according to the age of the child and the services provided through federally mandated intervention programs as well as state and local agencies. Across all ages, it is important for the child to have access to special recreation programs and social activities. Many younger children may want to access therapeutic horseback riding, karate, dance, and gymnastics programs as a part of their physical therapy program. Older youngsters and adults may want to participate in sports activities through such programs as Special Olympics, local disability sports organizations, or attend specially designed summer camps. Social activities such as coed dances and movie outings are favorites of older adolescents and adults.

All parents need an occasional break; therefore, local respite services are critical to how well families' function. Parents of a child with PWS are chronically fatigued and stressed by the constant vigilance required and the demands of behavioral challenges. Unfortunately, respite is increasingly limited for parents of children with special needs and even more so for those with PWS. Respite can take the form of a few hours, overnight, or even a period of days. When funded respite is unavailable, the social worker may want to help parents organize a parent-based respite cooperative. This serves not only the respite needs of parents but also the need for several children with PWS to socialize in each other's homes.

Education As stated previously, all US children with Prader-Willi syndrome are eligible for federally mandated early intervention programs from birth until the age of 3 years. Services are overseen by the state's developmental disabilities office and delivered by a designated agency or the local school district. Parents should be encouraged to enroll their child in such a program as soon as they receive a diagnosis. Physical and occupational therapy, speech and language services, nutritional services, and behavior interventions are available through these programs and should be instituted as soon as possible. In addition to specific therapies and activities, these programs are a source of support for parents. Developmental service agency case managers, school personnel, and other professional providers who are not familiar with PWS may call on the social worker to arrange an in-service training to familiarize school, clinic, or medical staff about the syndrome and answer questions regarding management. A day care for children with special needs may also be needed at this age. Some states provide ongoing services to qualifying individuals with a developmental disability beyond age 3 years, funded and delivered by other state agencies. The social worker is encouraged to help the family determine whether such services are available in their state.

Special education services through the Individuals with Disabilities Education Act (IDEA) serve the child from ages 3 to 22. Individualized Educational Plan (IEP) goals should anticipate and program for special services (see Chap. 11). For adolescents, transitional planning should begin on entering high school. Issues center around whether the child should pursue a diploma or a certificate of completion track, job training, and the transition from high school to a workshop or supported employment position. Transition planning should begin with prevocational and vocational planning during the first years in a high school setting. Vocational service staff will need considerable education about the special aspects of PWS (see Chaps. 13, 14, and 15).

Residential Options Discussion regarding the ultimate possibility of alternative living arrangements may be raised at this time as well. Making the decision to allow the young adult with PWS to move out of the family home to

another living arrangement is often a very difficult decision for the family and one that may take considerable time to make. The social worker should gently bring up the subject regarding future living plans early with the family. The family should be encouraged to discuss their feelings and fears with regard to this. Many parents need time to absorb the fact that it is "normal" for young adults to move out of the family home, even a young adult with PWS. Feelings of relief and feelings of guilt at that relief are not uncommon, along with fear that the staff of the home won't care for and about their child as well as the family does. Families will need assurance that the placement will provide complete control of food, constant supervision, and structured opportunities for social activities. The social worker will need to assist the family in contacting the local support person for alternative living arrangements. See Chap. 16 for more information on residential services.

Guardianship and Wills While all parents with children under age 18 should have wills, it becomes even more important when there is a child with a disability. It is critical for the parents to legally declare who should assume guardianship of the minor child in the event that both parents become deceased. Further, regardless of a family's wealth or assets, it is also critical that the family create a special needs trust to protect their child's future financial interests. This requires a very open and intimate conversation with those being asked to assume these responsibilities. Often the social worker can help the family rehearse ways to approach this issue or can join the family during the conversation, supporting them through some of the more emotionally difficult aspects such a discussion inevitably generates.

Guardianship and long-term financial planning become issues as the young adult approaches age 18. The laws of each state vary but are usually readily accessible on the Internet. For wills, special needs trusts, and guardianship/conservatorship issues, the social worker can provide parents with basic information and direct them toward the appropriate legal resource.

Conclusion

When a child has PWS, in addition to the usual parenting concerns, the family faces additional and often emotionally difficult issues requiring special information and services. The social worker is in a unique position to aid and support the family as they face the challenges and joys of parenting this child. Targeted social service intervention by the social worker can (1) help the family reestablish a working balance, while (2) providing education and guidance, and (3) providing support in obtaining and coordinating multiple medical and early intervention services for the affected child.

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A National Approach to Family Support and Advocacy

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Kate Beaver and Stacy Ward

Prader-Willi Syndrome Association | USA was formed in 1975 to unite parents, professionals, and other interested citizens to enhance the quality of life of those affected by Prader-Willi syndrome. The organization was born at a time when knowledge about the syndrome was sparce, medical professionals were just becoming acquainted with the syndrome, special education through the public school system was just being established (The Education for All Handicapped Children Public Law 94–142), and adult services were almost nonexistent. The need for research, dissemination of information, and family support was a driving force for the organization. In this era of little information and understanding, the needs of individuals and families in crisis were a constant demand and focus for the organization. This chapter provides a description of the various crisis issues that are presented by families or caregivers with a child, adolescent, or adult with the syndrome to the national PWSA | USA offices' trained Family Support Team.

Prader-Willi syndrome (PWS) often places great stress on the family and all persons who come into contact with the affected individual. The Prader-Willi Syndrome Association | USA national office offers a Family Support Team to provide wide ranging support and advocacy to families, teachers, and care providers. The Family Support Team provides education and training to medical providers, educators, and professional caregivers about the syndrome and advocates for the comprehensive needs of the entire PWS community. Constant requests for help are received at the national office through emails and telephone calls to a toll-free number. A trained Family Support Team member responds personally to these requests in a timely manner.

PWSA | USA's Family Support Team provides accurate information and comprehensive support for families at the time of their loved one's diagnosis. Later, the Parent Mentoring Program helps to connect families with "veteran" parents, mentors who have shared similar experiences. Parent Mentors are carefully chosen with each family's specific needs in mind and are committed to ensuring newly diagnosed families have access to the most up-to-date research material, educational literature, nutritional information, and therapy best practices. The Parent Mentor

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relationship is a 1-year formal relationship; however, the relationship with PWSA | USA can be maintained across the life span and serve as a resource as school-related concerns, medical issues, emotional crises, and adult services raise the need for further education and support.

The following exemplifies the many and varied concerns and requests for support that are presented by families or others advocating for a person who has PWS.

Advocacy for Services

Children with PWS are eligible for various services offered at the local level by national and state governments or their designees. When a child is diagnosed with PWS, it is important to obtain the assistance of a speech therapist, occupational therapist, and physical therapist to intervene in the area of low muscle tone or hypotonia. A majority of states offer these services through a local ARC organization or through the state Division of Disabilities. Usually, it is not a problem to establish eligibility for these services, but in some states these cases may be denied. Any denial of services should be appealed. When making an appeal, the resources that PWSA | USA can offer can be very helpful in resolving the issue and obtaining services. Once the deciding agency is educated about PWS and how it meets the federal disability definition, families are usually approved. One of these services that is not income based is for children under 18 years of age, it is a government-matched program called Katie Beckett, but may be named Cap C, or TEFRA in some states. The *Katie Beckett* program is for children under the age of 18 with disabilities or complex medical needs who are not Medicaid eligible because of their parent's income or assets.

Supplemental Security Income (SSI) is available to persons with qualifying disabilities whose income and resources do not exceed certain limits set by the US Social Security Administration. This usually applies to adults over 18 years of age who have PWS but can apply to children whose families also qualify for Medicaid or similar state medical insurance coverage. If the initial application is denied, the Family Support Team can assist in an SSI appeal. To win an appeal, it must be demonstrated that PWS is a lifelong and debilitating syndrome. This can be accomplished by working closely with the Family Support Team in gathering appropriate information for the appeal. The Family Support Team can assist with appealing denials for Medicaid, insurance coverage, Supplemental Security Income (SSI), and Social Security Disability Insurance (SSDI) by providing written appeal letters and supporting documentation.

Medical Concerns

While parents initiate a majority of our medical calls, the national PWSA office also receives calls from physicians, nursing personal, emergency room personnel, and intensive care units in the process of treating a person with PWS. These requests range from critical emergencies to basic medical issues that are unique to PWS. Medical issues can become exacerbated when the medical personnel is not familiar with PWS. The Family Support Team can facilitate consultations between PWSA | USA volunteer healthcare providers and an individual's medical team, emergency room staff, physicians, or other specialists.

While many queries are handled by directly speaking with the medical coordinator, PWSA maintains up-to-date resources for medical personnel as well as parents on an easily accessible website. The website contains the most recent information about general medical alerts, respiratory concerns, anesthesia considerations, weight management, as well as other medical and behavioral concerns. People with PWS have complex medical issues that often require a different kind of treatment than would be utilized in for individuals who do not have PWS. PWSA maintains a network of medical specialist that can give input or consult with local medical teams unfamiliar with treating PWS or facing an issue

known to require a different medical approach that would ordinarily be employed.

In addition to general medical concerns, morbid obesity can lead to both acute and chronic life-threatening medical problems often requiring crisis intervention to address the acute medical problems and to reverse the uncontrolled weight gain. The initial response to a call from the parents, who are aware and frightened that the eating is out of control, is to provide support for instituting the needed structure for controlling food access. If this is already being done, the Family Support Team can provide information on foods that can contribute to weight gain in persons with PWS and can provide parents with menus that address not only calorie control but also nutritional needs. In some situations, even though food is being controlled at home, the counselor can help in determining if the person with PWS is acquiring food from other sources and help to plan the appropriate preventive intervention. The Family Support Team routinely provides nutritional information and information about weight management to dietitians, school personnel, and a wide variety of other caregivers and providers not familiar with the syndrome.

Education Support

Often, when a child begins the educational process and the environment is not educated about PWS, major problems can arise, even as early as preschool. A primary goal for all parents is to obtain an Individualized Education Plan (IEP) for their child that is appropriate and addresses their child's unique needs related to PWS and learning. An IEP meeting can seem overwhelming and intimidating to the parents, even those with experience navigating special education. There are several online resources that parents are encouraged to explore to learn more about their child's rights.

NICHCY (www.nichcy.org), a federally funded information-clearing house on disabilities, has abundant information on the Individuals with Disabilities Education Act (IDEA), the US federal law governing public schools in the area of programming for persons with disabilities.

Wrights Law (wrightslaw.com) has information on how parents can manage the IEP world and key points in advocating.

The PWSAUSA website (pwsausa.org) offers webinars and other information to help parents deal with an often unresponsive educational system. Among the web-based resources currently available are the School Success Program comprised of six electronic toolkits including Behavior Challenges, Effective Advocacy, Homeschooling, IEPs, PWS Challenges and Solutions, and Special Education Law. PWSA also provides a transition book online for parents of high school-aged people with PWS.

Further, the PWSA Family Support Team can provide parents with educational materials to help prepare them for the IEP meeting and how to request a meeting and accurately document concerns and communication with the public school. Often a PWSA Family Support staff member, trained in Special Education Advocacy, will attend the IEP meeting through zoom or other media resources.

One area of the IEP that can cause parents' concern is that of requesting appropriate support and supervision. An experienced aide that is educated about PWS can often defuse or stabilize an environment. An aide can also be requested when the child with PWS is a serious food forager that may endanger the youngster and at the same time prohibits the child from fully accessing the curriculum. Nonetheless, this request is often met with resistance because of the added expense for the school and school district. The PWSA Family Support Team can assist in presenting information, educating, and attending meetings to help advocate for an aide in the classroom.

In addition, appropriate positive behavior plans for a person with PWS can be challenging to develop without the help of the Family Support Team. Children with PWS can have difficulty meeting the requirements of a classroom. Affected youngsters have tenuous emotional control and not infrequently disrupt a class with

a "meltdown." Often, the response to this behavior is based on a false assumption that the child with PWS has a control mechanism or can learn to gain control by receiving a consequence such as a threatened suspension. This sets up a negative spiral by increasing the child's anxiety that results in increases of the unwanted behavior. Another well-described characteristic of PWS is a range of behaviors that get labeled as "stubbornness." This may include "oppositional" behaviors, i.e., sitting down, refusing to move, or throwing something. Individuals with PWS can have difficulty prioritizing or sorting out major from minor issues resulting in anxiety, confusion, and, often, challenging behavior. Learning may also be complicated by processing delays, executive functioning issues, and ADHD or ADD.

To assist the administrative staff and the teacher in understanding the syndrome and offer positive suggestions for addressing the various behaviors that are manifestations of PWS, the Family Support Team provides resources in the form of webinars, zoom meetings, and written material. The Family Support staff speaks with the school representatives and the parents by phone first, to obtain a clear picture of the major concerns, which may be followed up with a conference call with the parents, school personnel, and the Family Support special education advocate. This process is designed to work toward developing a suitable positive behavioral and health and safety plan that is appropriate for the person with PWS.

In the USA, most children with disabilities are now integrated into general education classrooms. Currently, because of the violence in school in the USA, there is a "zero tolerance" discipline policy in many schools. Placement in a mainstream class brings a faster pace of learning and higher expectations, which heightens the pressure and performance anxiety in a person with PWS. It is also much more difficult to write a behavior management plan into the IEP that is practical for school staff to implement in a general education classroom. If the IEP does not have an appropriate behavior plan for the person with PWS, it increases the likelihood of legal problems. The Family Support Team, if involved early, can help by training school personnel and development of an appropriate behavior plan. If challenging behaviors cause the school system to seek legal intervention, the Family Support Team can assist in educating the legal system and advocating for the person with PWS.

Legal Concerns in the Public Arena

On rare occasions, the Family Support Team may be needed to help with a legal situation involving the person with PWS. Court cases can become complicated because the adult with PWS may appear to know the difference between right and wrong, and the legal system may not have a clear understanding of this syndrome.

The resources of the Family Support Team can be advantageous in educating the legal system about the manifestations of PWS and to advocate for a constructive resolution to the issue being presented.

Supported Living

Once a child with PWS begins to age out of the public school system, parents may begin the process of looking for an appropriate residential setting for their loved one with PWS. The PWSA website provides resources for parents to start this process. The transition booklet contains a list resources and options to consider. Also, the website provides a drop-down box menu that lists providers of residential settings along with healthcare providers by state or provider type.

One of the major challenges in finding placement is to find a residential setting that provides the least restrictive environment while maintaining strict food security. This is usually in a PWS-

specific group home, which means that the agency supporting the group home has applied and been granted the ability to lock and control food.

Consultation and trainings are available to residential providers and other support staff who need guidance or increased knowledge to support their client. Consultations may be provided in person, via telephone or teleconference. The Family Support Team works with organizations that express an interest in serving individuals with PWS and have inquired about training and program development.

Conclusion

Prader-Willi Syndrome Association | USA was formed in 1975 to unite parents, professionals, and other interested citizens to enhance the quality of life of those affected by Prader-Willi syndrome. PWSA | USA empowers the PWS community through shared experiences, research, education, advocacy, and support. That unwavering commitment remains the central focus.

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Advocacy Issues for School Discipline and Expulsion with Prader-Willi Syndrome

Barbara J. Goff and Barbara Y. Whitman

Introduction

Sara, a 7-year-old child with PWS, had been receiving home-bound instruction for 6 months as a result of disciplinary action taken in response to her classroom behaviors. These behaviors included wetting herself; throwing objects; property destruction; removing socks, shoes, and other clothing; engaging in self-injurious behavior (SIB); and demonstrating aggressive behavior toward her classmates. In the meantime, the school was seeking an appropriate alternate placement. Sara's parents felt that the placement identified and recommended was not at all suitable for their daughter. Sara's mother appealed the decision and engaged a lawyer. She and school staff determined they needed additional help to determine the most appropriate placement.

Sam, 14 years old and with PWS, had been receiving home-bound instruction for 6 months following several acts of aggression toward school personnel and attempting to leave school grounds. The school had made alternate placement recommendations, none of which were viewed as appropriate through the perspective of Sam's parents. Before engaging in a rigorous and lengthy mediation or a due process hearing, the school staff sought consultative help in reviewing the options for an appropriate educational program for Sam's placement.

Situations such as these are not uncommon for individuals with PWS, and both school professionals and families may feel perplexed and frustrated in approaching placement decisions following expulsion.

The Individuals with Disabilities Act (IDEA, Public Law 101–476, 1990; amended 1997, 2004) appears straightforward regarding the rights of students with disabilities to a free and appropriate public education and the provisions of multiple necessary supports to enable that education. For many students with disabilities, the process works smoothly and allows the student to optimally achieve his/her educational goals. Not infrequently, however, families of students with Prader-Willi syndrome (PWS) report significant difficulty obtaining necessary supports and

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services for their child, more than a reading of the law would suggest. This is particularly true when the student is demonstrating challenging behaviors in the classroom. Many families indicate an apparent unwillingness on the part of school personnel to understand the behavioral triggers and to modify the program and environment in order to minimize the occurrence of those triggers. Families often feel that, instead, the school employs ineffective and academically counterproductive disciplinary actions. Some parents go so far as to suggest a purposeful inducement of these behaviors aimed at precipitating a placement change.

On the other hand, school personnel frequently report that, in spite of their best efforts, the student with PWS has become far too disruptive or aggressive to be managed in the current placement. For example, the student may be throwing objects, hitting others, or running out of the school building into busy roads, even though a behavioral plan is already in place. All too often, the school's management of these behaviors is rooted in a misunderstanding of the syndrome and an unfamiliarity with best practices for supporting students with PWS and therefore concludes that the student is putting themselves and others in a potentially harmful situation, thus requiring an alternative placement. At the same time, some schools simply do not have the resources to appropriately and safely serve such a student in their setting and seek an alternative, more protective placement. This chapter reviews a number of typical scenarios reported by parents and school personnel, along with options under IDEA for improving the educational environment for students with Prader-Willi syndrome. The discussion applies to students with individual education programs (IEPs) as well as those who have 504 Plans.

Causes and Process for Disciplinary Actions and Alternate Placement

The national office of PWSA | USA receives numerous calls every year from families and schools seeking support for a student with PWS who is being disruptive and for whom the usual behavior strategies have been ineffective**.** Most calls are from parents requesting training for the school psychologist or behavior specialist on conducting a functional behavior assessment (FBA) on which to base a behavior intervention plan (BIP) for their child. They are worried that their child's behavior will lead to suspensions or expulsion from the current placement or school.

While parents routinely offer teachers and clinicians multiple resources about PWS as well as thorough descriptions of their child's specific behaviors, many feel their efforts are ignored. PWS is categorized as a "low-incidence" disability and therefore is rarely covered in teacher or clinical preparation programs. As a result, teachers and clinical staff are often lacking sufficient knowledge to allow them to recognize the unique behavioral phenotype of PWS.

Some examples of disruptive behavior typical of students with PWS include consistent refusal to complete assignments; sleeping through classes; refusal to transition; routinely interrupting the teacher or other students; severe skin picking requiring direct intervention; periods of screaming, yelling, or crying; and frequently leaving the classroom to address some concern or to escape the situation. Examples of life-threatening behavior include physical aggression directed toward teachers or staff, repeated attempts to leave the school building and grounds, and placing oneself in dangerous situations such as heavy traffic or unsafe neighborhoods. While these are all significant behaviors and should be addressed immediately and well before considering suspension or expulsion, in most instances, discovering (and avoiding) the child's triggers rather than relying solely on consequences (even food) to control behaviors has proven beneficial. Children with PWS are not aggressive without provocation. And objectively the aggressive response may be out of proportion to the situation, except in the mind of the student with PWS who has little impulse control.

Suspension is a frequently employed disciplinary action in response to property destruction, food stealing, disrupting the class, and hitting other students or school personnel.

Expulsion is usually the result of aggressive acts against school personnel. Neither suspension nor expulsion is an effective disciplinary tool for changing the behavior of a child with PWS, as much of their behavior is in response to inconsistent structure, inept handling, and inappropriate behavioral expectations in the school environment that suspension does not address. Attempts to "teach them a lesson" by using the presumed punishment of missing school rarely has the desired outcome and may have the opposite effect. Frequently children that have been suspended enjoy the time at home with a parent in a friendly environment that is absent the stresses experienced in the classroom; others may not even understand why they cannot return to school, thus vitiating the impact of suspension, while others may become distraught that their teacher doesn't like them anymore because they "did something bad." Too often, punishment is used in lieu of proactive strategies for students with behavior problems in spite of considerable research documenting its ineffectiveness. Without knowledge of PWS and well-established preventative strategies, students are suspended and expelled for engaging in behaviors that could have been anticipated and avoided or at least reduced in frequency, duration, and intensity. And, all too often, the most effective strategies involve simple environmental changes. The following are a few examples of how students with PWS may respond to common classroom situations and some potential solutions.

- A male teen was told that he couldn't go on a planned field trip as a consequence of recent unacceptable behavior. The field trip involved a picnic lunch. Upon receiving this news, the young man had an outburst, and while the teacher was calling for help, he grabbed the phone out of her hand and attempted, with some success, to hit her with it. While no serious physical harm resulted, the teacher was quite upset with the severity of the student's reaction and pressed charges. This extreme response to what for the student was perceived as taking away an opportunity for a picnic could have been avoided by choosing a more appropriate consequence for the recent nonfood-related behavior or by informing the parent ahead of time so that the student was not "ambushed" by being put in the perceived punishing situation of denial of a field trip with a picnic.
- A paraprofessional insisted that a student with PWS "hurry up" and put an (unfinished) worksheet away and move on to the next class. The child with PWS ripped up his paper, screamed at the paraprofessional, and stormed out of the room. The need to finish whatever they are doing is a well-described part of the behavioral profile in those with PWS. This would be better handled by keeping assignments manageable within the time allotted, having previously come to an agreement with the student about how to transition even when the assignment is not completed, or simply allowing the child to finish.
- A teacher failed to reassure a child who was perseveratively asking about an upcoming event. The child continuously interrupted the class to repeat her concern, and, given an inadequate response, she left the classroom and marched directly to the counselor's office where she insisted on using the phone to call her mother to get the information she needed. This student needed reassurance about the upcoming event, which could have been provided more effectively in a visual format. Often writing the date and time of the event on the board or providing the student with a written note addressing her specific concerns to which she can refer provides adequate relief from anxiety and reduces classroom disruptions from perseverative questioning.

An analysis of disciplinary action reports to the PWSA | USA over several years yields some interesting patterns . First, there appears to be no relationship between gender and typical disciplinary actions regarding students with PWS; however, males were more likely to be *expelled* from their current school-based program and be recommended for alternate placements. In most cases the precipitating events involved acts of aggression directed toward a teacher,

paraprofessional, or administrator. Placement in a separate special education class does not appear to be preventive or protective from recommendations for alternate placements.

Secondly, there was also no discernable pattern regarding cognitive ability. While the grade level at which such serious action is taken is typically middle or high school, even very young children have been recommended for alternate placements, as in Sara's story referenced above.

Further, in almost all cases of alternative placements reported to PWSA, school personnel—not other students—were the targets of aggression. These data suggest, and experts in the field have observed, that the teacher or other adult personnel are most often the source of frustration and, therefore, the recipient of the student's aggression. Hence, the notion that the student with PWS will invariably hurt other children may be largely unfounded.

Discipline Definitions Under Idea

Suspension Suspension from school can be used as a disciplinary measure for up to 10 school days per academic year at which time the school must proceed with a Manifestation Determination Review (MDR). This is considered a "short-term suspension" and is justified as a "cooling off" period during which the family and school can consider possible alternative placements if needed. Longer-term suspension or removal to an interim alternative education setting (IAES) for up to 45 school days can occur when the child has carried a weapon to school, possesses or uses illegal drugs, has inflicted serious bodily injury on another person, or if remaining in the current placement presents a substantial likelihood that serious bodily injury will result to others (the latter requires approval by a hearing officer). "Serious bodily injury" is defined as the infliction of extreme physical pain, obvious disfigurement, and protracted loss of or impairment of the function of a bodily member, organ, or mental faculty [1].

What Constitutes a Day of Suspension? One area of confusion for families is how days of suspension are counted. School districts interpret the law differently, including sometimes incorrectly. For the most part, schools attempt to avoid the 10-day mark as that sets in motion a formal process that is costly and time-consuming. Parents may be told, as they pick up their child after an outburst, that he isn't being "officially" suspended, though it is, by law "official" if he/she is being removed for at least half of the school day. Any amount of time of one-half day or more equals one full day and should be counted toward the 10-day limit for the school year. Any removal from the student's usual educational routine, whether it involves leaving the school site altogether or on-site removal from participation in his IEP designed program, might constitute suspension if removal is for more than half of a day.

Types of Suspension In-school suspension (ISS), an increasingly common alternative to sending a child home, is not counted as one of the 10 days *only* if the following conditions are met: (1) the student is afforded the opportunity to continue to appropriately progress in the general curriculum; (2) the student continues to receive the services specified on his IEP; and (3) the student continues to participate with nondisabled children to the extent he would have in his current IEP placement. However, if these conditions cannot be satisfied, then the ISS assignment constitutes a removal and counts as suspension. For example, if a child is sent to an alternative classroom or a staff office for more than half of the day to complete worksheets on his own, that would likely count as part of the 10-day suspension limit. Removal from any IEP services should be considered as potentially contributing to a suspension. Suspensions during extended school year programs (ESY, often referred to as summer school) are counted toward the total if removal involves a service written into the student's IEP. Suspension from bus transportation is also counted if transportation services were included in the student's IEP.

The 10-day suspension may be consecutive for a single occasion of misbehavior, although this is uncommon. More frequently, students are suspended for 1–3 days at a time. When suspensions are for similar misbehavior and are in relatively close time proximity, they can be viewed as constituting a pattern of exclusion and the 10-day rule applies. At the tenth day, the student is considered to have a change of placement, and a Manifestation Determination Review (MDR) hearing must be held.

Manifestation Determination Review

IDEA requires that a manifestation determination hearing be held within 10 school days of any decision to change the placement of a child with a disability because of conduct violations. The purpose of the hearing is to determine whether the behavior that led to the suspension(s) is a *manifestation* of the student's disability or the *direct result* of the school's failure to implement the IEP. The Manifestation Review Team typically consists of the members of the individualized education program (IEP) team, a special education administrator, an individual qualified to interpret evaluation data, and "other qualified personnel." The members of the MDR team should have personal knowledge of the student, special education, and the characteristics of the student's disability. Parents must be invited to attend the manifestation hearing as is their right when educational placements of their children are being discussed. The student should also be included in meetings pertaining to their educational program, if appropriate [1].

In the case of Prader-Willi syndrome, "other qualified personnel" could (and should) include an expert in Prader-Willi syndrome—someone who can review the records, observe the child, conduct interviews, and make a determination as to whether or not the cause for suspension was a result of the child having PWS.

The manifestation review committee must consider all records pertinent to the child's disability in relation to specific incidences of misconduct to determine if the misconduct was caused by, or had a direct and substantial relationship to, their disabilities. If the manifestation review committee determines that the student's misconduct was a manifestation of their disability, the student cannot be expelled.

Another responsibility of the review committee is to determine if the misconduct was due to an IEP (including behavior modifications) that was improperly implemented or if the child was in an inappropriate placement. If any of these conditions are met, the student cannot be expelled, and the current placement must be reconsidered. If the MDR committee determines that the behavior was unrelated to the student's disability and the IEP was properly implemented and the student appropriately placed, then the student is subject to a change of placement and any other disciplinary measures that could be imposed on a nondisabled student, including expulsion. The IDEA mandates that the school district provide special education services to an expelled student with disabilities, albeit in an alternative setting.

Parents may consider utilizing an educational advocate to assist them in understanding the law and process related to a manifestation hearing. Further, parents have the right to appeal the decision of the Manifestation Review Team, during which time the child remains in the prior placement from which he/she was suspended unless other options are agreed upon by the school and family. Removal for behaviors involving weapons or illegal drugs on school grounds, and those resulting in "serious bodily injury" to another person or presenting a substantial likelihood to cause injury to self or others, is allowable up to 45 school days. During this time, the school must provide educational services consistent with the student's IEP.

Preparing for a Manifestation Determination Hearing In preparing for a manifestation hearing, both parties must provide documentation supporting the contention that the behavior was, or was not, related to the student's disability, that

the IEP or behavior plan was or was not properly implemented, and that the student's placement was, or was not, appropriate. The burden falls primarily on parents to document that behavior was related to PWS or to inappropriate accommodations. Parents must be able to explain the relationship between the behavioral characteristics of PWS and the misbehavior that occurred. Parents should have expert documentation that explains the salient features of PWS in simple terms so the team can better understand how the disability and behaviors are related. Any references to the behavior characteristics of PWS described in the IEP should be highlighted to indicate that there was shared knowledge about the disability. It may be helpful for a family to provide pictorial representation of how the damage to the hypothalamus affects specific behaviors. For example, illustrating how the drive for food and the threat of being late for lunch if the assignment isn't finished would be a certain trigger for an outburst is directly related to underlying alterations in the hypothalamus. Or that an unanticipated change in the routine (particularly if it affected, or was perceived to affect, mealtime in any way) could create so much anxiety in the child that they run out of the classroom crying in search of a phone to call their mom. These scenarios seem extreme to the person unfamiliar with PWS but are relatively commonplace in school settings. Parents should provide any written documentation of phone calls or meetings with the school discussing the child's behavior and what was being done to intervene and support the child. Any requests from the parents for PWS specific training should also be presented. This can be contributing evidence that the IEP or behavior plan was not implemented as designed or that it was not current in reflecting the behaviors that lead to the suspension.

If parents feel the placement itself is inappropriate and can justify their position with evidence of their child regressing, withdrawing, or acting out as a result of the placement, it should also be presented at the hearing. Putting all this evidence together is a time-consuming, arduous task but made easier if meticulous records have been maintained along the way. This is one of the most unexpected yet most important jobs of parents of children with disabilities.

Assessment and Behavior Plans

When a student is subject to *any kind of discipline* beyond the short-term (up to 10 days) suspension, the school must conduct an assessment and develop a plan to address the student's behavior. Such an assessment is referred to as a functional behavioral assessment (FBA), with the plan referred to as a behavior intervention plan (BIP). If no plan existed prior to the disciplinary action, the IEP team must act immediately (within 10 school days) to develop the assessment and plan. If an FBA was done previously and a behavior plan exists, the IEP team must review and modify it as appropriate to address the current behavior. The intent of the FBA is to determine the purpose of the child's behavior: what drives it and what results. Is there a pattern, such as time of day, day of week, during specific classes, with certain teachers? For example, conducting an FBA may find that the student is most disruptive during math class. In this case, behavior is most likely a mismatch between expectations and ability. The student is not able, or believes they are not capable, of mastering the content. Out of frustration, materials are torn and tossed, and the student storms out if the room. The FBA may disclose that the previously used behavioral plan provided rewards for quietly remaining in the class; however, this is inadequate as the real issue is the curriculum content being presented is inappropriate.

IDEA does not provide guidance on how an FBA is to be conducted or its contents, but ideally it would be based on observational data and teacher reports rather than teacher reports alone. Observational data is important as much time, emotion, and effort has transpired prior to the suspension and manifestation hearing; the teachers may no longer be objective about the child and will rate the behavior as more frequent and more severe than it actually was. For example,

ratings on behavioral scales may say a student "never" complies or is "always" out of his seat, but such rating may be more an indication of frustration and exhaustion with the student rather than an accurate report.

During the FBA process, a specialist in Prader-Willi syndrome may be useful in assisting the school personnel to understanding the functions of the child's behaviors, which are intrinsic to the syndrome and may not be easily identifiable to those unfamiliar with the syndrome. Parents often have an "expert" role in pinpointing exactly what caused their child to act out and in developing effective behavior intervention plans. With proper training and support, teachers and staff may find that the student with PWS can be a positive addition to their class rather than a problem to be dealt with.

Parents' Right to Due Process

Parents' have the right to appeal any school decisions regarding a child's identification, evaluation, placement, or other provisions of a free appropriate public education for children with disabilities. Parents, or their attorney, by law may file a complaint against their state education agency (SEA) or their local education agency (LEA), specifically stating the reason for such action. Prior to a due process hearing regarding the complaint, the SEA must allow the parents and the SEA or LEA to resolve their disputes through mediation. This is a desirable option as it avoids the cost and time of a court trial and may serve to improve communication between parties. Generally, when cases make their way to the courtroom, the relationship between the school and the family has suffered a great deal of damage, with the ultimate victim being the student.

If mediation is unsuccessful, the parents can pursue their complaint through an "impartial due process hearing" conducted by the SEA or LEA. The participants in the hearing would include an impartial hearing officer, representatives from the LEA, the parents or guardians, attorneys for either party, and any individuals with special knowledge regarding children with disabilities who can present evidence or opinion pertinent to the case (e.g., an expert in Prader-Willi syndrome). Parents can continue the appeal process up to the federal court level, if desired.

Alternate Placements

Generally, the consideration of alternate placement begins with the student persisting in low levels of unacceptable behavior, such as work refusal, speaking out of turn, perseverating, skin picking, leaving the classroom, and falling asleep. Meetings are held, recommendations made, and modified behavior plans implemented nonetheless, yet the behaviors persist, perhaps even worsen. Finally, the child exhibits escalated aggressive or otherwise dangerous behavior viewed as the "last straw." The child is suspended indefinitely, most often remaining at home and is provided with approximately 2 h per day of instruction and special services identified in the IEP.

Even if it is decided that the behavior was directly related to the disability, if the school makes the case that the student presents a serious danger to self or others, an alternate placement may be sought. Until an alternate school-based program is mutually agreed upon, the current alternate placement remains the child's home. Unfortunately, while the school is investigating other options, the home placement can end up being an unintentional long-term placement, which does not serve the student well.

As with the examples of Sara and Sam at the beginning of the chapter, PWS specialists often become involved when the school has recommended a program that is viewed as unacceptable to a family. Often, the family has considerable knowledge and understanding about PWS that contributes to their concerns, and this knowledge absolutely should be included in determining placement. Typically, the alternative placements recommended are special schools for children with severe behavior problems that serve both young children and high school students. The

intent of these schools is to teach students how to control their behaviors so that they may return to a public school placement. These programs may have moderate success for children diagnosed with emotional and behavioral disorders. However, children with Prader-Willi syndrome do not respond to the behavior modification programs these schools typically utilize. While the programs are in place, there may be behavioral improvement, but these changes are not internalized as part of a permanent behavioral repertoire. When the program is withdrawn, the characteristic behaviors of PWS return.

An example illustrates how typical behavioral programs may be inappropriate—while extreme sounding, this is not an unlikely situation. One young man with PWS was in a residential school program where aversive therapy was used. The therapy included electric shocks, noxious odors, irritating sounds, water sprayed in the face, and other aversive consequences to reduce or eliminate undesirable behaviors. The students were placed at this school because they exhibited severe aggression and/or severe self-injurious behavior (SIB) over a long period of time. The school accepted only those students for whom every other effort at behavior change had failed. The targeted behaviors for the young man with PWS included lying, food seeking, and skin picking. The records indicate that he did demonstrate improvement during his stay at the school; however, when he was transferred to a group home for individuals with PWS, all of the targeted behaviors returned with similar frequency and intensity as existed prior to the use of aversive therapy, specifically shock therapy.

Are school districts being negligent or punitive in recommending behavior-focused schools? What is more likely is that school personnel simply do not understand the syndrome and view the student as a child with an eating disorder and behavior problems. Subsequently, they seek out the best programs serving children with similar characteristics. The professional staff at these special schools may be excellent and well-meaning in their willingness to work with children with PWS, but they too lack an accurate understanding of the syndrome. There is a dearth of school-based programs that equally address learning and behavioral needs. Either the primary disability is identified as learning or behavioral: rarely is there a program that recognizes that both conditions can exist in equal measure and, in fact, are inextricably intertwined.

In the case of Sara and Sam, every effort had been made to maintain them in their current public school placements, including employing consulting psychologists to develop functional behavioral assessments and behavior plans, increasing staff support, and decreasing the length of the school day. The missing ingredient was the failure to engage the services of someone with expertise in PWS, both to train personnel and to provide consultation on student specific issues. Most parents work well with school staff, providing whatever information is available, but they may be less able to articulate the broader technical concerns that affect the educational experience of children with PWS. Their focus is on their specific child. School personnel may erroneously view the parents' perspective as using the PWS diagnosis as an excuse, rather than explanation, for the student's behavior. The role of the PWS specialist is to bridge the gap in perspective.

Some of the most successful placements for students with PWS include schools for students with significant learning disabilities, classes or schools designed for students with autism or autistic-like behaviors, and residential schools specializing in PWS. The latter is the most difficult placement to get approved due to both scarcity and cost. As another option, schools may develop unique individualized educational programs for students who cannot handle larger classroom settings or who are in fully inclusive schools with no pullout or substantially separate class resources.

Prevention

The most distressing situation for students is when behavior problems become a crisis since intervention at the first signs of trouble might have avoided suspension and expulsion. Parents

of students with PWS can (and should) request that the school conduct a functional behavior assessment (FBA) and develop a behavior intervention plan (BIP) before the behaviors escalate to a point where serious disciplinary action is taken. Such a request may be met with resistance, as the school may say that they are not "required" to conduct an FBA and develop a BIP unless the child has been suspended for 10 days. However, under the law, schools have the option to conduct an FBA and BIP at any time if a student is exhibiting behaviors that may become serious enough to warrant suspension. Under these conditions, it is both wise and prudent to call for a team meeting to address the emerging problem. Furthermore, requesting this type of intervention proactively is helpful if and when the issue of suspension and expulsion arises, as it points to a general awareness that there was a serious problem that needed addressing. If the student has a behavior intervention plan in place that is not effective, then parents have every reason to request the involvement of a PWS specialist. If the school declines to involve an expert, stipulating that they have adequate expertise among their own staff, parents should ensure that their request for a PWS specialist becomes part of the written record.

Documenting the behaviors of concern, the suspensions (in all forms) being ordered, and requests for support and intervention also provides substantiation for maintaining the child in his current placement should a manifestation hearing be required. In fact, not conducting an FBA and developing a BIP when there are clear indications that they are needed can be considered a denial of a free and appropriate public education (FAPE).

Making the Best Decision for the Child

So, what now? In some instances, there is convincing evidence of the unsuitability of a particular placement. In others, where options are limited or nonexistent, there is a case for individualized programming. What is rarely acceptable is having the student remain at home with minimal instruction, no opportunities to socialize, and all care, including education, provided predominantly by the family. This is an unacceptable burden on both the student and the family.

Some schools are eager to provide the most appropriate education for the child with PWS, no matter what it takes. That was the case with Sam. With school personnel, family, and a PWS specialist working closely together, a carefully crafted program housed within the school was created. The school made a further commitment to pursue specialized training in Prader-Willi syndrome to ensure the success of this young man.

For Sara, and many other children, an alternative setting was and is a reasonable option. Sara's education team had lost enthusiasm and commitment for working with her, negatively impacting her education. However, a placement in a school designed to serve children with severe behavior problems with the goal of returning the child to their previous setting was not the answer. In seeking the proper alternative placement, all programs in the public school system that could provide the academic and behavioral supports needed and have staff who are willing to be trained in Prader-Willi syndrome should be explored. Where such programs do not exist, alternative schools designed for children with severe learning disabilities may be the right choice. These children tend to have concomitant behavior problems which the school personnel are trained to understand and address. And since these schools are not designed specifically for children with behavior disorders, their approaches to behavior management are often more individualized and flexible.

Eventually, Sara's family independently researched alterative placement options and presented their justification for placement to the school district. Sara was placed in a school for children with special needs and flourished. Sara still exhibits many of the behaviors that caused the transfer in the first place, but they are managed quite differently and are much less frequent and intense. For the first time, Sara is experiencing success, a sense of community, and a feeling

of safety. She looks forward to school and works diligently at being a well-rounded student. This same experience holds true for many other students with PWS who exit inclusive, or even self-contained, programs in public schools and find themselves in schools for children with a variety of learning problems.

While full inclusion is the current prevailing educational goal, some children find it extremely difficult to negotiate all the demands of a public school setting, even with special supports and services. Not all children with Prader-Willi syndrome are alike; for some individualized programs are required. Some students with PWS are successful in inclusion classes throughout their school career, while others are unable to handle the emotional experience of being different from their classmates. Many students with PWS do fine for the first several years of schooling, and then signs of unhappiness, perhaps even regression, begin to appear. This typically starts in third or fourth grade, when the academic and social gap between the child with Prader-Willi syndrome and those without disabilities widens dramatically. If, for whatever reasons, a school cannot modify its approach and create a positive and effective learning environment for a child, it may be time to look elsewhere and/or create something that does not yet exist.

Recommendations and Conclusion

Preventing disciplinary action for a student with PWS necessitates the good faith of all concerned: parents, teachers, administrators, clinicians, and anyone else involved in the student's education. Many of these youngsters go through school with only minor bumps along the way, while others seem to encounter major obstacles at every turn. For these students, specific attention must be paid to the unique characteristics of PWS and how they interact with the learning environment. When parents and professionals collaborate in good faith, amazing outcomes can result.

Here are some tips for parents for developing effective partnerships with school personnel so that disciplinary action may be prevented:

- Genuinely try to connect with the educators to help them in getting to know your child.
- Be a proactive participant on your child's team.
- Be an advocate for your child *and* the school.
- Validate the teacher's efforts; send written compliments with copies to their administrators.
- Ask the teacher when (daily, weekly, afternoons, evenings) and how (notes, phone calls, e-mail, personal visits) they would like to communicate.
- Volunteer to provide supervision on field trips to ensure that your child can successfully participate.
- Communicate, collaborate, and coach—even compromise—instead of criticizing and complaining.
- Pay attention to the early warning signs of discontent, from the teachers, the school, or your child.
- Assist in developing behavior management strategies that work for your child; clearly identify those that do not.
- Recommend specialized training (in addition to the training and materials you routinely provide) for personnel involved with your child before negative feelings and attitudes develop. The national office of PWSA-USA can assist you in locating qualified consultant/trainers.
- Search your school district for alternative programs and visit them. Should the school decide that they can no longer serve your child in the current setting, they will tell you what they believe to be an appropriate alternative—not necessarily apprise you of all the programs that are available. Consider out-of-district placements if the distance is not prohibitive.

Finally, families may need the help of an educational advocate, an attorney, and a PWS education specialist if they decide to appeal school decisions. Educational advocates are very helpful in interpreting laws and ensuring that families are aware of their rights as a parent. Attorneys with a specialty in education and disability law can direct the appeal process in the most beneficial

manner. Education specialists with an expertise in PWS can provide testimony and recommendations to the most appropriate programs and services.

Parents should not be expected to carry the entire burden of contentious placement decisions. Families should seek support in a timely fashion, as timely decisions can positively impact a student's entire school career. Teachers and professionals are entitled to adequate training, supports, and services to appropriately educate all children with disabilities. Prader-Willi syndrome is complicated and at times difficult to understand, and professional support is necessary. Every student needs a knowledgeable and cohesive team to support them and provide a free and appropriate public education in a safe and secure learning environment.

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Advocacy Issues: Sexuality and Prader-Willi Syndrome

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Barbara J. Goff

Sexuality Defined

Much has changed in the understanding of Prader-Willi syndrome (PWS) over the past 25 years. Better diagnostic tests have contributed to early diagnosis as the norm, the use of growth hormone treatment is commonplace, research on medications to curb obesity and reduce behavior difficulties has expanded greatly, more and more health professionals are familiar with PWS, and services for the individuals and their families exist where there were none before. While there is much more to be accomplished, individuals with PWS are now living healthier, happier, and longer lives. Yet there remain significant gaps in our understanding of the inner lives of people with PWS; one of the most glaring of these gaps is their experience as sexual beings.

Human sexuality is a broad term that encompasses biological, physiological, emotional, social, and spiritual feelings and behaviors. Indeed, sexuality is a "state of being" that incorporates gender and sexual identity, relationships, intimacy, and self-esteem as well as physical development and hormones [1]. While biologic sexual maturation may not be complete in the majority of individuals with Prader-Willi syndrome, that does not mean that a person with PWS is asexual. We are all sexual beings, including persons with PWS—who often dream about a romantic relationship, sometimes need intimate contact, and are always influenced by what they read, hear, observe, view on TV, and see on social media. This chapter briefly reviews the issues surrounding sexual development and identity, consensual and nonconsensual sexual behavior, sex education, and sexual abuse among individuals with Prader-Willi syndrome.

Sexual Development and Identity

Fertility Until recently, it was thought that infertility in the PWS population was universal. Parents, particularly mothers of individuals with PWS, have long quipped, "We are the only parents who worry more about our teen or adult children going into their dates' kitchen than into their

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bedroom!" When, in 1999, a woman with PWS gave birth to a healthy baby girl, a new reality emerged [2].

Subsequently, a total of five pregnancies have been reported resulting in four live births and one termination. Of the four known births, three women had the deletion form of PWS. Two of these women had children with Angelman syndrome and the third had a typically developing child. The remaining woman with the UPD form had a child who appears to be typically developing [2, 9, 10]. The fifth documented case describes a 26-year-old woman who had been recommended for contraception pills but refused. She became pregnant and chose to have an abortion.

There are two factors that appear to have a relationship with ability to conceive: having a menstrual period, even if infrequent, and normal weight at the time of conception. Current genetic understanding indicates that a woman with PWS due to maternal UPD is not at increased risk of having a child with a genetic problem or other known adverse outcomes assuming the father has normal chromosomes, but women with PWS due to a chromosome #15 deletion have a 50% risk of having a child with Angelman syndrome due to a deletion on the maternally inherited chromosome #15 (S. Cassidy, "personal communication", March 14, 2021).

Until recently, it also was believed that males with PWS were infertile given the lack of evidence that a male with PWS has ever fathered a child. This has recently been challenged by emerging evidence from several studies documenting normal sex hormone levels in some men with PWS. A recent study at the University of Florida assessed 24 males (ages 12–24) for puberty and fertility potential. Seven of these young males had normal levels of inhibin B and normal levels of FSH and LH, suggesting that it was at least hormonally possible for these young men to be fertile. None of these seven young men were receiving testosterone therapy at the time of assessment, and each appeared to be going through puberty normally. Without sperm counts and tests of motility, it is unclear whether these young men had the potential to father a child, but the door is open for that possibility. Normal sex hormone levels found in some males with PWS may be due to increased early medical and environmental management leading to normalized weight and fat mass, as well as the initiation of growth hormone treatment in infants (J Miller, "personal communication", March 10, 2021) although similar findings have been reported in males untreated with growth hormone. Given these findings, it is strongly recommended that any male with PWS engaging in sexual activity with females should be tested hormonally to determine capacity for reproduction.

Since the ability to adequately parent is extremely unlikely in even the most capable individuals with PWS, the vast majority of parents and providers wish to avoid the possibility of pregnancy altogether and do so, primarily, by preventing opportunities for sexual activity. However, it is incumbent upon those of us who support individuals with PWS to become more proactive in our efforts to teach birth control and healthy sexual behaviors, not just preach and protect. This discussion may become complicated when the individual with PWS wishes to become pregnant or father a child, which is frequently the case. The possibility of fertility is an important topic of discussion for parents and professionals and needs to be included in education programs on sexuality and birth control for young adults with PWS.

Sexual Identity Just as infertility has been assumed to be a given, so too has sexual identity.

It was once believed that individuals with PWS were asexual due to deficient hormonal levels [6] and that they did not have an interest in sexuality or sexual activity nor possess a sexual identity. Indeed, the prevailing thought has been that most individuals with PWS were essentially asexual. With improved care that has markedly increased the life span of affected individuals, we now know that adolescents and adults with PWS explore their sexual identity in much the same way as do typically developing teens and adults. Since there is no published data on sexual identity and PWS, the author conducted a survey with five professionals, each

of whom have 20–35 years of experience with individuals with PWS, regarding their observations and knowledge of the sexual orientation of the adolescents and adults with whom they have worked.

The results suggest that, as in the general population, the vast majority of adolescents and adults with PWS describe themselves as straight (heterosexual). However, there are individuals who identify as other than straight. In the combined experiences of the 5 professionals taking care of hundreds of individuals with PWS, 9 individuals were reported to identify as transexual (3 females to males and 6 males to females), 15 males identified as gay, and 8 women identified as lesbian. One male identified as bisexual. So, while not statistically significant given the hundreds of adolescents and adults in the PWS population, these numbers do inform us that people with PWS are not asexual and many are exploring, developing, and definitively identifying as other than heterosexual.

When considering the issue of sexual identity among individuals with PWS, it might be reasonable to question whether the individuals have a full understanding of what it means to identify in a particular way. For example, one provider reported on two individuals who identified as transgender for a period of time and expressed their identity with a change in name and dress but eventually resumed their birth identity as male or female. These specific individuals had a limited understanding of what it meant to be a transgender person, understanding it as a simple matter of a name and wardrobe change. On the other hand, three other individuals were reported to have fully adopted their trans identity and have lived consistently and fully as a trans person for several years.

According to a 2020 Gallup poll, 11.5% of the generation Z (born between 1997 and 2002) identify as bisexual, 2.1% identify as gay, 1.4% identify as lesbian, and 1.8% identify as transexual. It is important that current trends be recognized and acknowledged in our understanding of sexuality and PWS as these adolescents and adults are subject to the same changing attitudes and influences as their typical peers.

Sexual Activity That many persons with PWS engage in sexual activity is now well established, although inadequately researched. Parents, residential providers, and clinicians are increasingly coming forward with stories of their child's or client's interest and engagement in sexual activity. A survey of 17 provider agencies across 10 states serving 322 adults with PWS (age range 18–59) was conducted in 2010 by the author. The intent of the survey was to gather data on the sexual behavior of the individuals in their care and how the agency addressed sexual behavior among their residents. The results revealed that 57% of the men were in a romantic relationship with a female and 49% of the females were in a romantic relationship with a male. Of these relationships, 70% were with a partner who also had PWS, while 30% had a partner with a disability other than PWS. Most of these relationships were romantic and affectionate, but not explicitly sexual (28.6%), while 19.3% of couples engaged in kissing and fondling without sexual intercourse. A small number (8.7%) were engaging in sexual intercourse or oral/genital sex; however, only 7 of these 28 individuals were using birth control of any kind. The remaining couples were in an undefined relationship. It is likely those numbers will continue to rise with greater awareness and openness among families, care providers, and the individuals themselves.

This then raises a number of questions and concerns. What are the parameters of allowable expressions of sexuality? Who decides what is appropriate—parents, guardians, professional caregivers, or the individuals themselves? If sexual activity is permitted, what kind of protections should be taken? Who determines competency and how is it determined? Who does the teaching? Who does the monitoring? When an adult child with PWS lives away from home in supported care, how are parents assured that adequate protection is being provided? Conversely, how do providers ensure that they are protecting the rights of the individuals they serve to have a romantic and, even, a sexual life while keeping them safe from harm? Clearly, there is much work yet to be done around these issues.

Marriage/Cohabitation/Intimate Relationships

Many young women and men with PWS express a longing to get married and have children. In one study, 27 men and women with PWS ages 17–32 years old with a mean IQ of 75 were interviewed about their attitudes, feelings, and experiences with romance, sex, and marriage [8].

Consistent with the 2010 survey by the author, sexual activity in the form of kissing a romantic partner was reported by approximately 50% of the individuals. All of the males (100%) expressed the wish to be married while only 64% of the females felt similarly. Perhaps not surprisingly, 77% of males wanted hormone treatment to increase penis size while only 43% of women sought regular menstruation with the use of hormones. While the authors found no correlation between hormone levels and sexual interest, they did report that IQ correlated positively with interest in romance and dating [8]. This finding is significant in that the majority of individuals with PWS have IQ's in the mildly cognitively impaired and the borderline range.

This raises the questions of when couples with PWS want to get married or live together: what is their right to have this type of relationship? Is it so wrong for young adults with PWS to want a romantic and sexual life? Some parents ask, "Isn't it bad enough that they have to spend every day of their lives watching everyone around them enjoying the pleasure of eating? Do they also have to be deprived of this other basic pleasure and need in life?" On the other hand, others ask, "What is their potential for maintaining a long-term relationship?" The dilemma felt by parents is that while they wish their adult child to always feel loved and connected, they fear that they will be taken advantage of, or harmed in some way, by their choice of partner.

While cognitive or emotional capacity has never been the defining criteria for romantic relationships, cohabitation, marriage, or parenthood for the general population, it is nonetheless clear that cognitive capacity does impact the ability to understand right and wrong and distinguish allowable from disallowable moral and sexual behavior. A lack of understanding has led to problems of sexual charges against some young people with PWS. One example involved a mid-30s couple, both with PWS, who had been dating for two years. Although they were mutually consenting adults, when the young man's fondling of his girlfriend caused slight bleeding in her vagina, she was taken to the hospital emergency room, and he was charged with "felony, first-degree sexual assault and battery." A more sensitive and informed response would have been to provide counseling to the couple regarding their sexual activity.

Although systematic data is unavailable, social media documents that there are married couples with PWS, others who are cohabitating, and many more who are engaging in sexual activity. The provider agencies continue to support them in the same ways as they would for any individual with PWS, paying special attention to any relationship needs and concerns.

Like most issues, the answer to whether individuals with PWS should be married or engaged in sexual activity is not a simple one. Some of the intertwining issues include the following:

Family's Religious and Moral Beliefs Religious and moral beliefs certainly impact decision-making about sexual activity and marriage**.** Some families may strongly oppose sex outside of marriage, despite knowing that marriage may not be an option for their family member with PWS due to lack of maturity or the inability to maintain a long-term relationship. Moral or religious beliefs may likewise impact the degree of acceptance of their loved one living as a gay, lesbian, or transgender person. Furthermore, there may be a question of the individual experiencing undue pressure to adopt a particular identity or simply being taken advantage of for sexual purposes. It should be noted that the individuals with PWS, like many typical adolescents and adults, may struggle with their own strongly held religious or moral beliefs about sex outside of marriage and expressions of nonconforming sexual identity.

Choice of Partner How do parents or care providers protect a vulnerable adult from choosing

an unhealthy partner? What if one or both partners is overly controlling: physically, verbally, or emotionally abusive? It is critically important that parents and providers have an open and trusting relationship with the people in their care and work together to provide guidance and oversight should there be questionable interactions between a couple.

It often becomes worrisome when an individual with PWS is romantically involved with someone who does not have PWS. Such relationships are not unusual for two reasons: (1) many individuals with PWS do not want to be identified as having PWS; and (2) persons with PWS know that their non-PWS partner will have greater access to food and money. One parent reported that her daughter was dating a very nice young man that she knew through her workshop. He had a mild cognitive disability, did not have PWS, and routinely provided her with snacks, either brought from home or purchased with his money. The mother spoke with the young man about the harm he could be causing by supplying food to her already obese daughter. He replied that he understood and cared very much about the well-being of his girlfriend, but she had made it clear if he did not bring her what she wanted, she would not be his girlfriend anymore. While the example illustrates a frequent but relatively benign situation and one that caregivers can relatively easily handle, it becomes far more dangerous when a "normal" adult takes advantage of a person with PWS by trading food for sex. Again, the questions of protective parameters vs. "normalization" and who makes those decisions get raised.

Sexually Transmitted Diseases (STDs) How do parents and providers know the individual with PWS genuinely understands all they need to know about sexually transmitted infections and are adequately protected regardless of sexual identity? Here again it is important that parent and provider work together to provide education, support, and guidance.

What Is Appropriate Sexual Behavior? Movies, television, Internet websites, music videos, and social media portray increasingly sexualized ways people give and receive affection and pleasure. These depictions are influential on adolescents and adults with PWS who wish to engage in what they believe is "normal" romantic and sexual behavior.

With early intervention, growth hormone therapy, and improved weight management, many individuals with PWS are no longer easily identifiable as someone with a disability. Many individuals are also quite articulate and can easily convince someone in authority that they are capable of understanding right from wrong when in fact they are not. Great concern arises, therefore, that individuals with PWS may unknowingly make inappropriate sexual advances or engage in unlawful sexual behavior that results in criminal charges.

At this point in history, the issue of cohabitation or marriage is one to be made on a case-by-case basis. Many agencies will design a residential program that would support a couple who choose to marry or become life partners. Such a serious decision must be implemented only with a great deal of discussion, counseling, and education. Parent's support of marriage or partnership can be a powerful indicator of whether it will be successful.

Sexual Abuse

Social Media Technology has enhanced the lives of people with disabilities, enabling them to engage with others based on a shared interest or identity. Social media in particular enables people to connect with family and friends when direct contact is not an option. For individuals with PWS who may not, by virtue of having a rare disorder, have the opportunity to meet someone else diagnosed with PWS, social media can facilitate connections with others who have PWS anywhere in the world. Today's "pen pal" relationships take the form of FaceTime conversations, Facebook friendships, blogs, picture sharing, and organized online group activities. Social media also provides multiple sources of entertainment including YouTube videos,

movies, audiobooks, and music. Individuals can explore topics of interest that expand their awareness of the world, current events, and popular trends and investigate subject matter they do not feel comfortable exploring with family or staff, including information about dating and sexuality. The outcome of such searches can provide helpful information or lead to potentially dangerous situations.

Individuals with PWS who seek friendships, romantic relationships, and social acceptance through social media may experience bullying and are at risk to be victimized by sexual predators and others with ill intent. Two of the most frequently used social media apps are Snapchat and Instagram, both of which feature the ability to communicate pictures, videos, and words that can disappear within 3 s or only as long as the recipient is viewing the post. This makes it an excellent vehicle for inappropriate content to be shared while impossible for caretakers to track the source once the content "disappears." There is significant danger inherent in the immediacy and secrecy of such access. Teens and young adults with PWS have used these platforms and have been manipulated for money or sexual encounters.

Today, having a personal cell phone or smartphone and a computer is the norm. According to a 2018 national survey conducted by the Common Sense Media, 53% of children own smartphones by the age of 11 with 89% of teens overall owning smartphones. It is likely the statistics are similar for adolescents and adults with PWS.

Restricting access to all Internet-based technologies is not a viable solution; therefore, it is important that parents and care providers are meticulously aware of how the individual with PWS is utilizing the Internet and social media. It is equally important that the individual with PWS knows they need not rely solely on the Internet or social media for information about relationships and sexuality that loved ones or providers will be sensitively available for such conversations.

Conversations such as these start with talking with the individual about the potential dangers of various social media platforms and apps and coming to an agreement about which of these should be blocked or limited. Have the individual share their password(s) in case of an emergency, with the understanding that parents and caretakers will be respectful of the person's privacy unless there is a suspicion of potential danger. Fortunately, there are many social media safety programs available.

Physical Abuse and Exploitation According to the 2015 National Intimate Partner and Sexual Violence Survey, 43.6% of women will have been sexually assaulted in their lifetime. This includes attempted or completed rape (21.3%), coercion by nonphysical means (16%), being forced to penetrate someone else (1.2%), and unwanted sexual contact (37%) such as being groped, fondled, or grabbed. For men, 24.8% have been sexually assaulted in their lifetime, including attempted or completed rape (2.6%), coercion by nonphysical means (9.6%), being forced to penetrate someone else (7.1%), and unwanted sexual contact (17.9%). Sexual assault is more common in younger individuals with the percentage of sexual assaults (completed or attempted) of women occurring before age 25 which is 81.3%; by age 18, 43.2%; by ages between 11 and 17, 30.5%; and by ages 10 and under, 12.7%. For men, it is 70.8% by age 25; by age 18, 51.3%; by ages between 11 and 17, 25.3%; and by ages 10 and under, 26% [13]. As disturbing as these figures are, the statistics for people with intellectual disabilities (ID) are far worse.

Joseph Shapiro, a reporter of the National Public Radio (NPR), conducted a yearlong investigation into sexual abuse and individuals with intellectual and developmental disabilities (IDD). Drawing from unpublished data from the US Department of Justice, he reported that people with IDD were seven times more likely than their nondisabled peers to be sexually assaulted. For women with disabilities, the number was 12 times as likely. This is a significantly higher rate than has been previously reported. Consistent

with what has been reported in the past, 86% of the assault victims knew their abuser [11].

A 2012 national survey of individuals with disabilities, conducted by the Disability and Abuse Project, revealed that 66.6% of all people with intellectual/developmental disabilities have been victims of abuse and over one-third of those were sexually abused more than once [3]. In another survey, approximately 80% of women and 30% of men with an intellectual disability reported having been sexually assaulted with half of the women having been assaulted more than ten times. Sadly, only an estimated 3% of sexual abuse involving people with developmental disabilities are ever reported [5].

Allegations of sexual abuse by persons with PWS must be carefully investigated by professionals with expertise in PWS to rule out false accusations. Lying, confabulation, and storytelling are trait characteristics of PWS. There have been a number of cases of false allegations of sexual abuse made by persons with PWS. The falseness of accusations usually becomes apparent with adept questioning focused upon learning what the individual hopes to gain from the story. Several years ago, the author was asked to be an expert witness on behalf of a young woman with PWS who was alleging serial sexual abuse against her stepfather that occurred during her childhood. After some initial hesitation based on previous experience with similar reports in which there was clear confabulation, combined with the opportunity to examine the details of the case, to listen to the woman's taped statement, and to speak with people who knew her well, the request to testify on her behalf was accepted. The key detail in that decision was that the young woman's recounting of the incidents was consistent over time with none of the usual embellishments for effect. In addition, it was clear that no benefit would accrue to her as a result of pursuing her allegations. Having previously examined numerous allegations of abuse involving people with PWS, it is usually quite apparent in a very short period of time that there is something the individual hopes to gain from the story being told. More will be said of this later.

Individuals with PWS are especially vulnerable to being sexually exploited and abused for the following several reasons:

1. An uncritical trust of everyone—Many individuals with PWS have an emotionally and socially innocent nature.
2. An increased dependency on others—Affected individuals often lack control over their environment and thus are forced, due to their situation, to place an inordinate amount of trust in those who care for them.
3. An increased vulnerability to anyone who befriends them—Often it is difficult for those with PWS to socialize and communicate; thus they are more vulnerable to anyone expressing kindness. Many abusers use the "special friend" and "shared secret" approach.
4. An increased vulnerability to bribes—Anyone who would give food secretly to a child or adult who has Prader-Willi syndrome would be considered a friend for life, even if this friend was sexually abusive.
5. A normal need for physical attention, often coupled with a lack of adequate sexual education or appropriate outlets—Children with PWS typically enjoy giving and receiving affection. However, many students with PWS are not included in school-based sex education programs, as it is assumed the information is not relevant or will not be understood. As they grow into adolescence, the typical socializing and dating experiences are not available to them. As a result, there may be problems with inappropriate sexual behavior arising during this period and into adulthood.
6. An increased fantasy life—Being more socially isolated than the average child, people with PWS often build up great romantic fantasy lives of which a molester can take advantage. Also, their inability to think abstractly in many cases means they will be less able to make appropriate moral and social decisions.
7. An increased likelihood to be in settings where other adults have control over them—Foster homes, group homes, institutions,

camping programs, and other supervised settings are all potential settings for molestation.
8. Many children and adults with disabilities are not taught about nor afforded the right to privacy and learn not to expect it.

The perpetuation of abuse against individuals with disabilities, including those with PWS, is also aided silently by two factors: (1) most persons who are molested do not tell due to fear, guilt, shame, and concern for others; and (2) most parents and professionals do not suspect—or do not believe the individual when they do tell.

Failure to report occurs with greater frequency in those with cognitive disabilities compared to a nondisabled population. Many have insufficient language or understanding to adequately report. They may not even perceive or experience that what occurred was wrong. The perpetrator often threatens harm if the abuse is reported. As a result, many victims experience an acute behavioral deterioration. The possibility of sexual abuse should be considered as a possible etiology but is often overlooked in individuals with intellectual disabilities, resulting in inappropriate treatments for wrongly diagnosed conditions [12]. Preventing sexual abuse of people with PWS requires multiple strategies, the center of which should be a carefully considered sexual health education program.

Prevention of Sexual Abuse

Preventing sexual abuse of people with PWS requires multiple strategies, the center of which should be a carefully considered sexual health education program. Sexual abuse of individuals with intellectual and developmental disabilities is a relatively common area of research and a frequent topic among parents and professionals; strategies for *prevention* of sexual abuse are largely ignored. Typical sex education curricula for children address "stranger danger," who can see or touch various parts of one's body and who to talk to if confused about what is okay and what is not. Current curricula do not typically address the more complex or subtle contributors to sexual abuse such as the desire to feel accepted and loved that contribute to vulnerability. While we want individuals to trust and feel safe with the people entrusted to care for them, they must also be able to identify an "unsafe" care provider, recognize "special" treatment that is also abusive, and identify an abusive touch that may also feel good. This confusion is often heightened since data indicate that the majority of time, the molester is someone known to the youngster and someone on whom they depend. More refined criteria must be developed that incorporate the more sophisticated circumstances under which sexual abuse can occur.

There is an erroneous belief that anyone choosing to work with people with disabilities is inherently a good person and will not cause harm. While this may be true for the vast majority of workers, it is not universal, as statistics on abusers will attest. Sadly, a molester is typically someone known to the individual and someone on whom they depend, and people with disabilities are often in settings and in the care of the very people most likely to abuse them.

Educators and school-based personnel are all too often perpetrators of abuse. While there are some indicators of the "typical" abuser, any employee or volunteer could be a molester. Sexual predators are frequently described as excellent teachers and are often well liked by students. Educators who have access to students before and after school or other opportunities to be alone with a student (e.g., music teachers, coaches, teachers who provide after-school tutoring, transportation personnel) frequently abuse students, especially students with disabilities [14]. It is incumbent upon school administrators to monitor situations where students may be alone with a teacher, and all teachers and staff should be trained to recognize signs of potential sexual abuse and be aware of their colleagues' interactions with students.

Adults with disabilities are especially vulnerable to those upon whom they depend for their

day-to-day care. Even so, one study found that care providers of persons with disabilities typically have limited knowledge of disabilities and hold negative attitudes toward persons with disabilities [7]. Most agency orientation programs address staff's legal mandates to report suspected abuse but do not explore their attitudes or misconceptions about the people in their care. Employers of residential day program and transportation services must recognize that the individuals they hire may be predisposed to engage in sexually abusive behavior with the individuals in their care and must develop curricula and protocols to reduce or eliminate that risk.

Agencies, schools, and clinics providing services to individuals with disabilities must take greater responsibility to ensure that a prospective employee does not have a record of sex abuse. This is easily accomplished by conducting a search on the National Sex Offender Public Website (NSOPW), as well as conducting other routine criminal record checks. Second, an assessment should be made of the knowledge and attitudes of prospective employees and ensure they receive the necessary education and training prior to assuming their work responsibilities.

Compliance is a highly valued trait among persons with disabilities, especially those diagnosed with PWS, and goals for increased compliance are often seen written in educational and program plans. At the same time, disabled individuals must be taught how to appropriately advocate for themselves, starting at an early age and continuing throughout their lifetime. As young children, this means encouraging self-awareness and choice making. As they progress through school, it means participation in decision-making about their classes and activities. At the high school level, it means actively participating in designing their high school and post-high school living and vocational plans. As adults, self-advocacy should encompass all aspects of their lives. Persons with PWS need to be given the training, support, and opportunities to appropriately self-advocate, including on issues pertaining to sexuality and relationships.

Sexual Health Education in School

Even though most states and the District of Columbia mandate that public schools provide some form of sex education, students with disabilities are often excluded from these classes for a variety of reasons. In one survey, only 44.1% of students with mild ID and 16.8% of students with moderate to profound ID received sex education. Teacher's opinions about the benefit of sex education ranged from 68% positive and necessary for students with mild ID to 25% for students with moderate to profound ID [4].

Some of the barriers to sexual health education include the following:

- Societal belief that people with disabilities are asexual, particularly those with intellectual disabilities, worse yet that their sexuality is viewed as deviant
- Strong desire to protect young people with disabilities from sexual knowledge should it influence them to engage in sexual activity
- Parental concerns regarding content and potential effect as well as religious and cultural beliefs and attitudes
- Inadequate teacher's confidence, knowledge, and training to provide instruction in sexual health
- The lack of valid and reliable sexual health education for individuals with various disabilities and cognitive levels
- The lack of federal funding specifically designed for students with disabilities based on comprehensive sexual health education

Young people with PWS need and deserve sex education, as evidenced by this author's experience reading letters and notes created by and shared within a group of teens with PWS. The content of these communications was replete with sexual thoughts and feelings and contained explicit sexual language and imagery. Boys typically focused on sexualized content fueled by their apparent access to pornography, whereas girls appeared more interested on romance. In attempt to discern whether these teens under-

stood what they were writing, the author posed a number of questions which confirmed they were indeed interested in sex and were seeking sexual encounters. It was clear these adolescents needed education and guidance from a knowledgeable and supportive adult about what it means to be in a romantic and/or sexual relationship.

Teachers and school clinicians should have a greater understanding of the sexual, social, and emotional development of their student with PWS so that conversations around areas of sexuality and sexual expression can be informed and sensitive. Ignoring the student's experience increases the likelihood the student will be teased, bullied, or shamed, or more severely, be sexually victimized, exposed to sexually transmitted infections, or become pregnant. Coaches and physical education teachers should be aware that the boy with PWS may be teased for his small penis, high voice, or lack of facial hair. Males with PWS may try to compensate for this is in multiple ways; this author worked with one young man who always wore a necktie so he would not be mistaken for a girl. Teachers should be aware that the young lady with PWS might be caught unaware in a conversation with typically developing girls about menstruation and stories about when each girl "got her period." Young people with PWS need information and language so that they more easily negotiate these typical school encounters.

A common complaint of teachers is that some of their students with PWS (and other disabilities) will be sitting at their desk with "their hand down their pants." A typical response of the teacher is to speak with the student about the correct time and place for such behavior without knowing whether the student understands about what behavior the teacher is referring or why they are being chastised or reprimanded. Similarly, other physical or sexual behaviors such as a boy patting a girl's behind, trying to kiss her, or insisting she is his girlfriend are often met with disciplinary action for being "inappropriate." Responses or interventions that do not incorporate the individual's disability can inadvertently leave them feeling confused and shamed, teach them that self-pleasure is bad, or imply that having a girlfriend or boyfriend is not an option. Opportunities for problems increase in middle and high school settings which are frequently fraught with sexual inuendo, language, and behavior. Typically developing students are often good at "getting away" with inappropriate behaviors, whereas the students with disabilities are more likely to get "caught" and less likely to understand what they did wrong.

Traditional school-based sex education curricula have not been developed to address students with disabilities, much less students with PWS whose differences often include physical development, incomplete puberty, and reproductive issues. Participation in a traditional sex education course may not be appropriate if there is concern about the student's differences being insensitively highlighted, if the student does not feel safe to ask questions, or if the student lacks the ability to ask questions appropriately.

An appropriately designed sexual health program for students with a disability should focus on teaching body part names and function, self-care, and the relational aspects of sexuality. Curriculum that teaches body part names will also help the student to more accurately describe a sexual encounter made by a fellow student or by school personnel. Small group instruction may be the most appropriate forum for sex education, where students can also practice how to establish various types of relationships, whether friendship or romantic. Similar to students with autism, students with PWS have deficits in social cognition and need concrete, skill-based training and opportunities to practice various social skills including as how to hold a conversation, how to ask another person to dance, and how to appropriately rebuff unwanted attention. Small group discussions can help students understand why it is not okay to touch an individual on their butt or breasts at school, what consent means, and how to know if someone is taking advantage for their own gain.

The challenge for educators, disability specialists, and parents is to adapt current curriculum so that it better serves the disabled population, incorporating the type and amount of sexual health education that is appropriate to each student's needs and understanding and incorporating these into their individualized education plan.

Having been immersed in issues of sex education and people with intellectual disabilities since the 1970s, this author can attest to the fact that access to sexual content and sexual awareness among individuals with IDD, including young people with PWS, has grown exponentially. Unfortunately, attitudes about sexuality and people with disabilities and policies and procedures within school districts and service agencies have not acknowledged nor responded to this changing demographic. Parents currently bear the full responsibility of educating their child on all matters regarding sexuality and often need support and resources for themselves as well as to share with the many professionals who are an integral part of their child's life.

Sexual Health Education for Adults

Service providers in the adult care system, particularly residential providers, have a mandated responsibility to address issues of sexuality for adults with disabilities in their care. Often, providers are as hesitant as educators to venture into the complex arena of sexuality. In the 2010 survey conducted by the author, the majority of provider agencies took a "Don't Ask, Don't Tell" approach. Of the 17 residential service agencies sampled, only 4 (23%) provided routine sex education to the individuals they served. Another 11 (65%) agencies would provide some sort of sex education training only after an individual began to have a romantic or sexual relationship. The remaining two (12%) agencies provided abuse prevention training only.

As these data indicate, few service providers take a proactive approach in providing sexual health education to the individuals in their care. Some of the reasons are the same as those discussed in the previous section on sex education in schools. Agencies do not want to discover that a resident has been sexually abused or became pregnant on their watch, so they tend toward restricting opportunities rather than providing appropriate and adequate education and training. The following are some of the issues provider agencies struggle with when dealing with sexuality and sexual expression for the adults with PWS they serve:

What Are the Parameters of Appropriate and Allowable Expressions of Sexuality? This is dependent on the individual and his/her desires and capabilities. Where there is a question regarding competency to knowingly engage in sexual activity, the provider is responsible to conduct an assessment to determine competency and provide supports and supervision accordingly. If the adult resides with their family, there are agencies that can provide such assessments.

Who Decides: Parents or Professional Caregivers? Parents, quite naturally, wish to guide the lives of their children according to specific religious or moral beliefs; providers, while respecting those beliefs, must also adhere to established agency and state standards of care, which include matters of sexuality and sexual expression. While there may never be complete agreement as to what is best for the individual with PWS, there must always be a process and a dialogue that keeps in focus the health, happiness, and wishes of the individual with Prader-Willi syndrome.

Again, if the individual is an adult in a residential program, competency must be established. If the person is deemed competent, then the policies of the agency and/or state must be adhered to. In some agencies, sexual activity is prohibited within the residence itself, but other options may be explored. In general, individuals who are deemed incompetent to consent to sexual activity will receive a certain level of supervision if sexual activity is suspected. In most cases, the agency is obligated to provide sex education commensurate with the capacity of the individual(s) to understand and benefit. This includes the use of protective devices.

What If the Parent Has Guardianship? Having a guardian does not mean that an individual and the service provider must abide by their demands regarding sexual expression. The specific control over decision-making by a guardian varies from state to state and is unlikely to include decisions

pertaining to sexual activity and choices, unless the individual has been assessed to be unable to provide informed consent.

If Sexual Activity Is Allowed, What Kind of Protection Should Be Used? Any type of protection to be utilized during sexual activity would need to be medically approved and recommended and be of the type that the individual is most likely to use consistently and effectively. In all cases, condoms should be used to prevent STDs.

Who Does the Monitoring? Generally, it is the residential staff that monitors any developing romantic or sexual relationships. They do so in order to ensure the safety and well-being of the individuals involved. Typically, there are agency guidelines to follow and supervisory staff to provide oversight with regard to sexual activity. If a sexual relationship is perceived as harmful, it most certainly will be stopped and investigated immediately. If it is assessed to be consensual and not harmful physically or emotionally, then most agencies would seek to provide education and counseling as appropriate.

When an Adult with PWS Lives Away from Home, How Are Parents Assured That Protection Is Being Utilized? If a sexual relationship is being permitted after recommended assessments are completed and appropriate education provided, then the provider agency can only depend on the willingness of the individuals to be honest and forthcoming in their discussions of safe sex. If agency staff suspects failure to follow recommended and agreed-upon protective measures, they may prohibit sexual activity until or unless the situation is rectified. Some women with intellectual disabilities, including PWS, have actively sought out opportunities to have sex in order to become pregnant. This underscores the need to be proactive in our efforts to be open and to listen to their desires, hopes, and dreams.

Who Provides Sexual Health Education? The teaching of sexual information is delivered by the person(s) deemed to be most appropriate for the individual(s). For example, if a person has severe cognitive deficits, a direct service staff person with whom the individual has a close relationship could function as a conduit to introduce the individual to an educator/counselor who specializes in sexual health education for people with cognitive disabilities. The staff member would reassure the individual that this counselor is safe to talk with in private. If needed, the staff person could attend the sessions with the individual in order to provide clarification and follow up. In this way, staff are protected so that accusations of inappropriate behavior or information may be avoided. If the individual is living at home, parents should seek out specialized sex education programs for people with intellectual disabilities. Any sexual health education training should focus on self-care; building relationships, both platonic and romantic; and fulfilling lifestyles that do not necessarily include a romantic partner or children, not just issues related to sexual activity.

While proactive sexual health education should be provided as matter of course, when a couple appears to be moving toward a sexually intimate relationship or is asking about becoming sexually active, the agency (or parents) should seek resources for counseling, not just for the purpose of discussing sexual activity but to help the couple explore their relationship first so that issues of consent and mutual desire for intimacy can be established.

It is also important to note that many individuals with PWS are perfectly happy simply having a boyfriend or girlfriend, even one that lives miles away. These relationships should be encouraged through helping the individual make phone calls, write letters, text, and use FaceTime and Facebook to support the relationship. Not all individuals are interested in sexual activity and are contented to get together every year or so at conferences.

The Role of Direct Service Staff In considering the role of direct service staff in sex education, certain realities need to be addressed. To begin, the staff is made up of individuals who range in age, have varying degrees of education, represent different cultural beliefs and practices, may speak

English as a second language, hold different religious beliefs, may view the adults in their care as childlike, and more. This can cause confusion for the residents should they seek information or counsel from a favored staff member who may tell them to "just say no" or "it is a sin," or "it is nothing for you to think about," or "ask your parents." While that last bit of advice may be prudent, there is the possibility that the individuals have intentionally chosen not to speak to their parents about their questions and concerns. It is best that the staff have an approved resource for the individual to access that provides appropriate training and guidance that is consistent with best practice and agency policy.

Allegations of Abuse: Real or Manipulative

A well-documented characteristic of children and adults with PWS is purposeful lying when angry in an effort to hurt or get revenge against the perceived offender. Or the individual is seeking a particular outcome from the allegation. And, as mentioned, many have active fantasy lives to compensate for the lack of social and emotional stimulation in their real lives, which can lead to made-up stories about adults that may seem real in their minds. As a result, some parents and providers have been unfairly charged with having committed physical or sexual abuse.

As an example, a young adult male recently admitted as a resident in a group home alleged multiple instances of abuse, including sexual, against his house manager. His stories were quite elaborate and kept growing with each telling. The manager was relieved of his duties until the investigation was complete which had already taken several months before seeking consultation from the author. Objectively, the young man's stories were too fantastical to be believed, but the adults (e.g., police officers, investigators, counselors, and his mom) were convinced that these horrific things must have occurred as there would be no way this young man could come up with such explicit details of sexual abuse, drug use, and more. The prevailing attitudes were that he was too young, too innocent, and too cognitively impaired to make up such stories. A review of "volumes of documents" pertaining to the case was conducted specifically with an eye toward what the young man was hoping to gain from these allegations. It quickly emerged that he wanted to be removed from the residence and returned to his home with his mom who was all too eager to find fault with the residence. While he was living with his mom, he was provided with love, attention, and an overabundance of food. While the alleged allegations were deemed unfounded, nonetheless the damage was done. This well-meaning house manager, who provided the structure and limits the young man required, became a target and suffered in a myriad of ways. Nor is this story unique. Staff working with individuals with PWS worry constantly about allegations of abuse, physical, verbal, and sexual, as they are frequently made. More often than not, the individual is looking to get the staff person removed from the residence (i.e., fired) out of revenge for some sense of wrongdoing or for being too "strict" regarding the menu plan or other house rules. Parents know all too well the damage of allegations of abuse, as they too are frequent targets and have endured unexpected investigations by state agencies. Fortunately, the vast majority are determined to be unfounded; but the experience is devastating and the fear of it reoccurring remains.

If a parent has a son or daughter in residential or vocational placement or is considering doing so, do not ignore the very important topic of sexuality and sexual expression in discussions with the provider. Parents should inquire as to any policies, procedures, or prohibitions the agency may have with regard to sex education and sexual activity prior to their child's placement.

Conclusion

Ensuring a quality life for a person with Prader-Willi syndrome has layers of complexity, as well as ethical and legal issues that are not always easily resolved. The rights and responsibilities regarding sexuality will continue to require a

combination of an open mind, common sense, and ongoing dialogue among parents, caregivers, and, most importantly, the person with Prader-Willi syndrome. There are new questions about fertility, the desire of young adults to explore sexual identity and sexual intimacy, and a continued concern over increased risk for sexual abuse. It is the intention of this discussion to highlight these new understandings of sexuality for individuals with PWS and to advocate for the provision of a comprehensive sexual health education program for children and adults.

First, there must be a recognition of the tremendous diversity among people with PWS, increasingly so with the routine use of growth hormone and early diagnosis. They represent a range of cognitive abilities, appearance, race, culture, language, religion, health status, and life experience—all of which affects their future goals and aspirations. We have seen individuals graduate from college, maintain supported employment, live in a variety of supported residential programs, participate in numerous community activities, and engage in a myriad of meaningful relationships. We can no longer make any assumptions about what may lie ahead.

Where care is shared between families and providers, both parties must come together with the individual to determine what makes sense for that person at a particular point in time and to determine what resources the individual may need to engage in informed decision-making about their lives, including matters of sexuality. It is not simply a question of *who* decides for them, but a matter of *how* decisions are made.

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Pharmacotherapy in Prader-Willi Syndrome

22

Janice L. Forster

Introduction and Historical Perspectives About Pharmacotherapy in PWS

Prader-Willi syndrome (PWS) is a rare, genetic, obesity-related disorder with an occurrence of about 1 in 15,000–30,000 births. It is a disorder of genomic imprinting that results from the loss of paternally expressed genes from 15q11 to q13 region. In the majority of cases (about 60%), it results from a de novo deletion of the paternally derived region. In about 35% of cases, it is caused by maternal uniparental disomy 15 in which both chromosome 15s are inherited from the mother. The remaining subjects have a defect of the imprinting center that controls the expression of the activity of the imprinted genes in the region, or they have translocations or inversions of chromosome 15 [12]. PWS is characterized by hypotonia; poor suck and feeding difficulties at birth leading to failure to thrive during infancy; hypogonadism and hypogenitalism; growth and other hormone deficiencies leading to short stature, small hands and feet, and decreased muscle mass and strength in early childhood; and reduced cognition with behavioral problems (temper tantrums, emotional outbursts, excessive repetitive and compulsive behaviors, anxiety and mood problems, and self-injury). Food seeking and hyperphagia develop in early childhood, leading to obesity and obesity-related morbidity and mortality without strict oversight and external controls. Psychological food security (FOOD SECURITY), environmental food control, and dietary and exercise management have been life-saving but challenging for families to implement across the life cycle. Many of the manifestations of the syndrome are due to hypothalamic dysfunction. Individuals with PWS respond to treatment with growth hormone, resulting in increased stature during childhood and adolescence, a change in body composition (decreased fat mass, increased lean body mass), and improvements in cognition and well-being at any age.

Compared to the evidence base for growth hormone treatment in PWS, the evidence basis for pharmacotherapy of hyperphagia, behavioral problems, and mood disorders associated with PWS is limited. Historically, only a few single case studies have been reported on the use of haloperidol or carbamazepine to manage behavioral problems and fenfluramine to manage hyperphagia [54, 94, 124, 144]. Because fluoxetine was initially studied to manage appetite before it was found to be effective as an antidepressant, there was hope that it might decrease

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food intake in PWS. But off-label use for weight loss in the typical population was disappointing, and the incidence of adverse effects was greater than placebo [125]. With the release of additional selective serotonin reuptake inhibitors (SSRIs), nonselective serotonin-norepinephrine reuptake inhibitors (SNRIs), and second-generation antipsychotic agents (SGAs) also known as "atypical neuroleptics," additional medications have been added to the pharmacological tool kit for the management of phenotypic behaviors and psychiatric comorbidities associated with this rare syndrome. Currently, polypharmacy (use of multiple medications at the same time) is a common finding in the treatment of persons with PWS. Despite the use of many classes of medication, there are few published studies exploring indications for treatment, dosing parameters, and adverse effects. There is only one study (unpublished) looking at pharmacogenetics in PWS [34] and two recent publications examining pharmacogenetics and pharmacodynamics [42, 43].

The use of SSRIs in persons with PWS was historically associated with two key scientific publications. The first paper suggested that PWS provided a genetic link to obsessive-compulsive disorder (OCD) [33]. This led the clinical community to believe that SSRIs were the treatment of choice for the excessive, repetitive, and compulsive behaviors associated with the PWS phenotype (State et al. 1999). In fact, there are a few case reports indicating improvement in these symptoms after treatment with fluoxetine [24, 148]. But because OCD symptoms typically require high doses of SSRIs for remission, these dosing parameters were applied by psychiatrists (and other medical professionals) to persons with PWS. Subsequently, in her role as psychiatric consultant to the Children's Institute (the only inpatient rehabilitation program in the country managing morbid obesity and psychiatric disorders in PWS), the author noted a pattern of mood and behavioral activation that was identified in approximately one-third of individuals with PWS of all ages who were receiving SSRIs at the time of hospitalization [44]. Sometimes, prescribed doses were too high, for example, fluoxetine 40 mg twice daily, and a dose reduction led to improvement. In other cases, mood stabilizers or antipsychotic medications were required for stabilization. Current pharmacological intervention with SSRIs has focused on the use of low doses to manage cognitive, mood, and behavioral symptoms associated with PWS with the mantra of "start low, go slow." Despite the fact that the "OCD in PWS" hypothesis has been challenged and refuted by others who have suggested a developmental paradigm for these phenotypic symptoms of excessive repetitive and compulsive behaviors ([61, 153] (Genes)), the impact on research and clinical care persists to this day, and SSRIs continue to be recommended for treatment of phenotypic symptoms associated with PWS.

The second paper reported the discovery that one of the snoRNAs in the critical, imprinted region of chromosome 15q11-q13 coded for the antisense gene is essential for the proper editing of the serotonin 2C receptor [70]. This led the PWS community to believe that "SSRIs were good for people with PWS." In fact, the author knows of a few cases where infants with PWS had been prescribed fluoxetine with the belief that it conferred some protective value.

This chapter will present an overview of studies looking at pharmacological management in PWS; efficacy of pharmacotherapy in PWS; pharmacogenetic, pharmacokinetic, and pharmacodynamic factors related to drug selection, drug metabolism, drug dosing, and schedule of administration in PWS; adverse events associated with different classes of medication and their effects on body systems; and recommendations for pharmacological intervention in PWS going forward.

An Overview of Pharmacotherapy in PWS

Despite the extensive use of psychotropic medications in persons with PWS of all ages to manage behavior, mood instability, and psychosis, the evidence base for pharmacotherapy is lacking. There are very few studies that have explored the rationale for medication selection, a scheme for dose titration, the duration of treatment needed for symptom resolution, the incidence of adverse effects, and most importantly the pharmacological strategies for prevention. The following are

three considerations that have complicated a systematic approach to evaluating pharmacotherapy in PWS:

- The neurobehavioral and neuropsychiatric phenotype of PWS is complex and varies across development.
- Although phenotypic characteristics are determined by genetic subtype, there is considerable individual variability within these categories.
- Many of the characteristic phenotypic behaviors can be managed through environmental manipulation.

The best description of the current approach to pharmacotherapy is *selective symptom management*. Psychotropic medications are used frequently to target phenotypic behaviors of hyperphagia, repetitive and ritualistic behavior, disruptive behavior (temper tantrums), impulsive aggression, skin picking (self-injury or self-mutilation), and excessive daytime sleepiness. With one notable exception (N-acetylcysteine for management of skin picking), there is little specificity for efficacy across multiple classes of medications. Comorbid psychiatric diagnoses (cyclic psychosis or bipolar disorder, depression with or without psychosis, intermittent explosive disorder, and anxiety disorders) present with treatment challenges and often require more than one class of medication for management. Many medications have a global effect on behavior by buffering the interaction between the person and the environment. Frequently, this approach dampens all behaviors, including adaptive ones. Overall, there appears to be inadequate attention to building coping strategies to help the person manage stress or teaching skills to caregivers to manage behavior more effectively. Figure 22.1 presents a schematic of tiered interventions for successful management of phenotypic behaviors [46].

The most comprehensive article on pharmacotherapy in PWS to date is the Bonnot meta-analysis of the literature from 1997 to 2014 covering 102 patients from 241 case reports [8]. The authors concluded "The pharmacological approach of behavioral impairment in PWS has been poorly investigated to date." The following discussion will review the results of surveys, published meta-analysis from literature review, clinical reports of case series, and individual case studies published in the scientific literature. Also included are scientific abstracts from the PWS-specific literature (e.g., PWSA Gathered View Newsletter), as well as unpublished abstracts presented at scientific meetings at the Prader-Willi Association USA (PWSA USA) and International Prader-Willi Syndrome Organization (IPWSO).

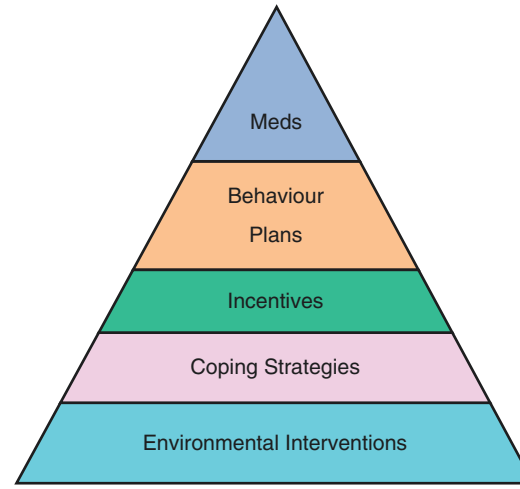

Fig. 22.1 The PWS intervention pyramid

There are several surveys of psychotropic medication use among persons with PWS of different ages across different settings. These are reviewed in sections "Vanderbilt Parent Survey", "Residential School Survey", "PWSA State Chapter Survey", and "NIH Rare Disease Natural History in Prader-Willi Syndrome Consortium".

Vanderbilt Parent Survey

In 2006, Roof and Dykens released the results of their parent survey on psychotropic medication use in PWS and published their findings in the PWSA Gathered View Newsletter [118]. The medication survey was completed by 86 parents regarding their child with PWS, ages 8–51 years (mean age = 24 years). Table 22.1 shows the pattern of medication use.

Table 22.1 Frequency of medication use in a PWS sample, *n* = 86, ages 8–51 years (mean = 24), from the Vanderbilt Parent Survey

Medication class	Frequency
SSRIs alone	33%
SSRI + antipsychotic	17%
SSRI + antipsychotic + anticonvulsant	17%
SSRI + anti-anxiety or antidepressant	9%
Antipsychotic alone	11%
Antipsychotic + other	12%

Key: *SSRI* selective serotonin reuptake inhibitor

Psychiatric diagnosis, genetic subtype of PWS, doses of medication, and medication side effects were not reported. As noted in Table 22.1, most participants (76%) in their study were taking an SSRI plus other agent(s), and 33% were taking SSRIs alone; 46% were taking an antipsychotic plus additional medication(s), and 11% were taking an antipsychotic medication alone.

Residential School Survey

A 2016 clinical survey (pilot data, unpublished) identified psychotropic medication use in a population of adolescents with PWS attending a residential school program (Table 22.2). There were 25 adolescents, ages 15–21: 6 females and 19 males.

Although 60% of individuals were receiving antipsychotic medication for management of behavioral difficulties associated with the syndrome, the number of adolescents with psychosis was surprisingly low. Antidepressant medications (SSRI + SNRI) were prescribed in 40% of individuals, and antianxiety agents (buspirone + alpha-adrenergic agonists, beta-adrenergic antagonists, and hydroxyzine, an antihistamine) were prescribed in 36%. The use of these medications corresponded to the frequency of mood and anxiety disorders diagnosed among this group. Of interest, there were no prescriptions for benzodiazepine anxiolytics.

The results of this survey involving adolescents with PWS in a residential school setting are similar to the prescribing pattern of using SGAs "off label" in the USA. Several studies of both Medicaid and commercially insured recipients found similar results with approximately two-thirds of children and adolescents in the USA receiving SGAs prescribed as "off label," that is, without a psychiatric diagnosis to justify the use of this class of medication [89, 107]. Diagnostic comorbidity among children and adolescents was very high for "off-label" prescribing, and prescribers were less likely to be child and adolescent psychiatrists in younger, more vulnerable children [100, 107]. FDA guidelines for use of antipsychotic medication in children and adolescents are based on evidence of safety and effectiveness in managing the symptoms of tics and psychosis or severe behavioral problems associated with autism spectrum or disruptive behavior disorder resistant to other forms of treatment [57].

Table 22.2 Frequency of psychotropic medication use among adolescents with PWS in a residential school program, *n* = 25

Psychotropic medications	Frequency
Antipsychotic agents	60% (sum)
SGA (atypical)	56%
FGA (typical)	4%
Antidepressants	
SSRI + SNRI	40%
Antianxiety agents	28% (sum)
Buspirone	4%
Minor tranquilizers (lorazepam, clonazepam)	0%
Alpha adrenergic agonists	12%
Beta-adrenergic blockers	8%
Hydroxyzine	4%
Stimulants (methylphenidate, dextroamphetamine)	24%
Anticonvulsant mood stabilizers	2%
Lithium	8%
Antiparkinsonian agents (Cogentin, Benadryl)	8%
Amantadine	4%
Sleep aids (melatonin)	4%
Desmopressin	16%

Key: *SGAs* second-generation "atypical" antipsychotics, *FGAs* first-generation "typical" antipsychotics, *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitor

PWSA State Chapter Survey

In an unpublished pilot study from a PWS state chapter, 27 families having a person with PWS completed a survey regarding medication administration. The ages of the subjects ranged from 6 to 49 years with a mean age of 22 years. Seventy-four percent were living at home with their family, while the others lived in group homes. Sixty-three percent of the patients had the 15q11-q13 deletion, 26% had maternal uniparental disomy (UPD) 15, and the genetic status was not known in 11%. In this survey, 26% of people with PWS had never used medications to treat conditions related to PWS. Table 22.3 summarizes the medication utilization data from these 27 individuals with PWS in this state chapter survey.

Among all those reporting, antidepressants and antianxiety agents were used most commonly (37% each), with antipsychotics the next most common (30%), followed by mood stabilizers (26%) and stimulants (15%).

NIH Rare Disease Natural History in Prader-Willi Syndrome Consortium

As part of a multisite registry or consortium (University of Florida, University of Kansas, University of California (Irvine), and Vanderbilt University) sponsored by the National Institutes of Health (NIH) Rare Disease Consortium for Prader-Willi Syndrome (PWS) and PWSA-USA, the use of psychotropic medications as well as supplements and nutraceuticals in 355 persons with PWS was reported for up to 10 years during scheduled clinic visits [11]. The age range of the PWS cohort in this study (NIH PWS Registry) was 2 months to 70 years (average age 13.4 years). The average BMI was 25.6. There were 197 females and 158 males. The race/ethnicity of the population was 93% Caucasian. The distribution of genetic subtypes was 61.3% deletion, 35.5% UPD, and 3.2% imprinting center defect. Data were obtained from medication forms completed at the time of the clinic visit and from retrospective record reviews. Target symptoms, doses, or treatment outcomes with medications was not always indicated, although it is possible to infer that patients with the most medication changes were the least likely to have achieved symptom improvement. These data provide a glimpse of the psychotropic medications used in persons with PWS. It is an important data set; the largest of its kind derived exclusively from a US cohort sampled over time.

According to the data in the NIH PWS Registry, 165 out of 345 patients were prescribed a total of 482 psychotropic medications over time from 2005 to 2013. Of the total number of patients, about half were receiving psychotropic medications. The actual number of psychotropic medications prescribed to the PWS patients is itemized by class and listed in Table 22.4.

The percentage of patients prescribed psychotropic medications by class is listed in Table 22.5.

Table 22.3 Medication utilization data from 27 persons with PWS ages 6–49 (mean age 22)

Class of medication	Percent of respondents
No medications	26%
Antidepressants	37%
Antianxiety agents	37%
Antipsychotics	30%
Mood stabilizers	26%
Stimulants	15%
Omega-3 fish oils	44%
Coenzyme Q10	30%

Table 22.4 Number of psychotropic medications by class prescribed to patients in the NIH PWS Registry

Medication class	Percent prescribed
SSRI	30.3%
SNRI	1.9%
Antianxiety	6.4%
Atypical antipsychotics (SGAs)	18.0%
Typical antipsychotics (FGAs)	2.3%
Anti-epilepsy/mood stabilizer	16.0%
Mood stabilizer/lithium	0.8%
Anticholinergic agents	1.2%
Stimulant	7.5%
Non-stimulant	8.1%
Sleeping aid	2.1%

Key: *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitor, *SGA* second-generation antipsychotic, *FGA* first-generation antipsychotic

Table 22.5 Percentage of patients from the NIH PWS Registry receiving psychotropic meds by class

Antidepressant/ antianxiety	N	Antipsychotic/mood stabilizer	N	Anti-epilepsy/mood stabilizer	N	Stimulant/ non-stimulant	N
SSRI	**146**	**SGA**	**87**	**Anti-epilepsy**	**77**	**Methyphenidate**	**36**
Fluoxetine	56	Risperidone	37	Topiramate	32	Ritalin[a]	20
Sertraline	37	Aripiprazole	26	Valproic acid	17	Concerta[a]	8
Citalopram	23	Quetiapine	14	Phenobarbital	6	Focalin[a]	6
Escitalopram	15	Ziprasidone	7	Carbamazepine	3	Metadate[a]	1
Paroxetine	12	Paliperidone	2	Oxcarbazepine	4	Daytrana[a]	1
Fluvoxamine	3	Olanzapine	1	R-etiracetam	4	**Amphetamine**	**11**
SNRI	**9**	**FGA**	**11**	Lamotrigine	5	Adderall[a]	5
Nefazodone	1	Haloperidol	3	Gabapentin	2	Dexedrine[a]	5
Venlafaxine	4	Loxapine	4	Tiagabine	2	Vyvanse[a]	1
Desvenlafaxine	1	Thioridazine	3	Zonisamide	1	**Non-stimulant**	**39**
Imipramine	1	Chlorpromazine	1	Phenytoin	1	Atomoxetine	5
Clomipramine	2			**Mood stabilizer**	**4**	Modafinil	33
Other	**13**	**Anticholinergic**	**6**	Lithium	4	Armodafinil	1
Bupropion	12						
Trazodone	1	Benztropine	3			**Opioid blocker**	**2**
Anxiety hypnotic	**31**	Diphenhydramine	3				
Benzodiazepine	8					Naltrexone	2
Clonidine	8						
Guanfacine	5					**Sleep aid**	**10**
Buspirone	6						
Hydroxyzine	4					Melatonin	10

Key: *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitor, *SGAs* second-generation "atypical" antipsychotics, *FGAs* first-generation "typical" antipsychotics
[a]Brand name used. Bolded numbers in the table are subtotals for each medication class

When available, the age at which a medication was first prescribed was indicated. When the number of medications in each class was assorted by the decade of life in which they were first prescribed, an interesting trend emerges as seen in Fig. 22.2.

SSRIs were used extensively in the first decade of life, and this trend more than doubles in the second decade. In fact, in several single cases from the NIH PWS Registry, fluoxetine was first prescribed at age two years in one case and at age four years in another; sertraline was first prescribed at age four years; and citalopram was first prescribed at age five years. The lower age limit for use of SSRI medications established by the FDA is 12 years, except for fluoxetine, which is the only SSRI permitted at age 8 years for depression provided that psychotherapy alone was not effective. Similarly, fluoxetine is indicated for anxiety at ages below 6 years if psychotherapy administered alone for 12 weeks was not successful and then only if fluoxetine is added to ongoing psychotherapy. It is also specified that if fluoxetine at a dose of 1–2 mg/day up to 5–8 mg/day is ineffective, then sertraline or fluvoxamine can be considered (see www.medicaidmentalhealth.org).

During the first decade of life, the use of stimulants, non-stimulants, and SSRIs is about equal. The use of non-stimulants in infancy is due primarily to the use of modafinil to promote wakefulness, and the use of stimulants in the school age years is most likely to manage inattention in the classroom. The number of AE (anti-epileptic) agents used in infancy is due to the management of seizure disorder. Although SSRI use was noted in the first decade as previously discussed, the peak age of first prescribing SSRI medications was between 10 and 19 years of age, and this correlates with parent reports of behavioral manifestations of anxiety in PWS, such as repetitive questioning, compulsive and repetitive behaviors, and impulsive/disruptive tantrums which are prevalent during this decade. There was also a

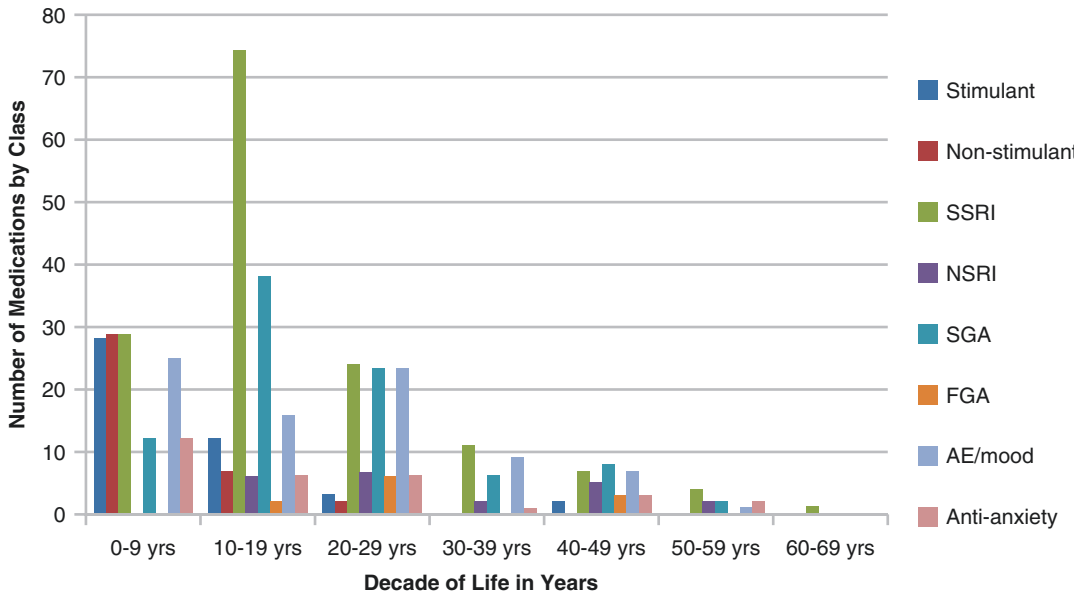

Fig. 22.2 Number of medications first prescribed by decade of life in the NIH PWS Registry. (Key: SSRI selective serotonin reuptake inhibitor, SNRI serotonin-norepinephrine reuptake inhibitor, SGA second-generation antipsychotic, FGA first-generation antipsychotic)

peak for the use of SGA (atypical antipsychotic) medications at this time, and these agents are approved for use for impulsive/aggression and irritability in children. Another peak in the first use of anti-epileptic/mood stabilizers occurs in the third decade (20–29 years). These agents are also used for impulsive aggression (valproic acid), skin picking (topiramate), and mood stabilization (valproic acid, carbamazepine/oxcarbazepine, lithium).

The NIH PWS Registry has defined age categories as follows: birth–<2 years (n = 39, 11.0%), 2–<5 years (n = 56, 15.8%), 5–<12 years (n = 105, 29.6%), 12–<21 years (n = 77, 22.0%), and ≥21 years (n = 78, 22.0%). Figure 22.3 displays the age at which medications of each class were first prescribed according to the age categories defined in the NIH PWS Registry.

In Fig. 22.3, medication use was corrected for the number of persons in each NIH PWS Registry cohort. For example, among the 105 children with PWS at 5 <12 years, 47.6% of them were first prescribed SSRI medications. As previously noted, the lower age limit for prescribing SSRI medications established by the FDA is 12 years of age, indicating that SSRI use in PWS is not in keeping with FDA guidelines. Further, in the 12–21-year cohort of 77 children, adolescents, and young adults, 70% of them were started on SSRIs, 33% were started on SGAs, and 25% were started on AE/mood stabilizers. In the >21-year cohort of 78 PWS adults, the utilization of SSRIs decreases to a level commensurate with use during childhood, but nearly equal to use of SGAs and AE/mood stabilizers. There is a linear rise in the use of both SGAs and AE/mood stabilizers from 5 to 12 years into adulthood. Because these medications are prescribed for mood instability, one wonders if the extensive use of SSRIs is driving the phenomenon of mood and behavioral activation [51, 104].

A comparison of psychotropic medications prescribed in a large data base (more than six million) of non-PWS children, adolescents, and young adults ages at 3–24 years in the USA was reported by Sultan et al. [138]. In the 2018 report, stimulant prescriptions were the most frequent and peaked around age 11 years. Antidepressant medication use rose steadily in this population through the developmental period and was high-

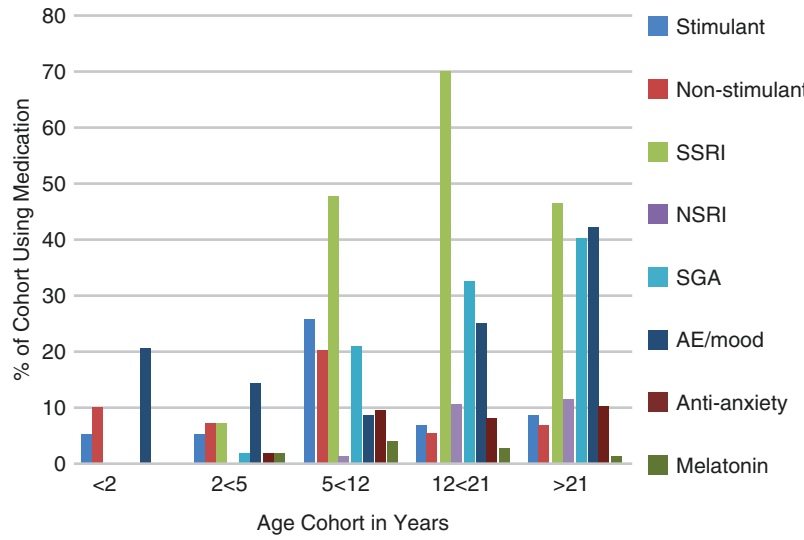

Fig. 22.3 Drug utilization by age cohort. (Key: SSRI selective serotonin reuptake inhibitor, SNRI serotonin-norepinephrine reuptake inhibitor, SGA second-generation antipsychotic, FGA first-generation antipsychotic, AE anti-epileptic (anticonvulsant))

est around the age of 24 years. Prevalence of antidepressant use was the same for both sexes until age 13, after which prescriptions for females were higher, and this is a well-known trend. Antipsychotic use was lower than both stimulants and antidepressants, and it peaked around age 16 years [138].

The NIH PWS Registry data were also analyzed to capture the degree of polypharmacy. The medications identified were *not* necessarily the number of medications needed to clinically stabilize the person. Further, these data were not factored according to age (younger registrants were less likely to be receiving more than one medication) or the number of years of follow-up in the clinics (older registrants were more likely to have used a number of psychotropic medications over time). A complex picture emerged when itemizing the number of psychotropic medications used in the NIH PWS Registry cohort and the frequency of patients receiving psychotropic medications by class. Among those receiving psychotropic medications, the use of one psychotropic medication was reported 47.4% of the time. The frequency of medications by class is found in Table 22.6.

The use of two psychotropic medications was prescribed 26.9% of the time. The most common combination was SSRI + SGA (25.8%) followed by SSRI + AED (11.2%). Further, some patients were receiving multiple medications of the same class, for example, Ritalin and Concerta, Prozac, and Zoloft or Abilify and Seroquel, or a similar class, for example, Focalin and Provigil, Celexa, and Wellbutrin or Risperdal and Loxapine. The use of multiple medications increases the potential for adverse

Table 22.6 Distribution of single agents prescribed as identified by medication class

Class of medication	Single agents (percent of total)
SSRI	30.6%
SNRI	1.3%
Other	0.6%
AHD	5.1%
SGA	11.5%
FGA	1.3%
ACH	0.6%
AED	19.7%
Lithium	0.6%
MPH	8.3%
AMP	2.5%
Non-stimulant	0
Modafinil	15.3%
Melatonin	2.5%
Naltrexone	0

Key: *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitor, *Other* other antidepressant, *AHD* anxiety hypnotic drug, *SGA* second-generation antipsychotic, *FGA* first-generation antipsychotic, *ACH* anticholinergic agent, *AED* anti-epilepsy drug, *MPH* methylphenidate derivative, *AMP* amphetamine derivative

events. There is little evidence for increased efficacy when combining medications of a similar class [95, 96]. However, there are some notable exceptions. More than one type of stimulant may be used across the day to improve duration of efficacy in ADHD. The use of an SSRI and an SNRI might be required to augment the effectiveness of antidepressant treatment. Further, lithium may be added to oxcarbazepine treatment to manage the side effect of hyponatremia. Finally, low-dose aripiprazole may be used to manage hyperprolactinemia associated with risperidone and similar antipsychotic medications. Also, it is possible that two medications of the same class were prescribed during a cross titration/taper from one agent to the next. As the number of medications used in combination increases, greater is the risk for drug interactions and adverse events. For example, patients were receiving three or more psychotropic medications 13.9% of the time. When attempting to identify prescribing patterns of drug utilization by medication class from the data provided, an overly complex picture emerged (Tables 22.7, 22.8, 22.9, 22.10, 22.11, 22.12, and 22.13).

This complex picture of medication utilization in patients with PWS suggests that there is no common pathway to medication selection. SSRIs, SGAs, AEDs, and modafinil were the most common agents prescribed both as single medications and in various combinations. Given the incidence of cyclic mood disorder in PWS, it is surprising that lithium carbonate was used so rarely. The age of the registrants may have played a part, although lithium has been used successfully in youth without PWS to treat bipolar disorder [110]. Polypharmacy using greater than or equal to two medications at one time was reported in over half of those patients receiving psychotropic medications at the following frequencies: two medications (26.9%), three medications (13.9%), four medications (6%), five medications (3%), six medications (0.6%), seven medications (1.5%), eight medications (0.3%), and nine medications (0.3%) taken together. This increases greatly the risk of drug-drug interactions and adverse events. Over time, it appears likely that medications are added but rarely discontinued when expected results are not obtained.

In summary, analysis of these data from the NIH PWS Registry provides a glimpse into the prescribing practices across the USA. It is evident that SSRIs are selected first for medication management of symptoms manifested by patients with PWS. Anti-epileptic medications are the next most prevalent medication, with a bimodal distribution that both reflects seizure management in the young and mood management across the life span. Atypical neuroleptics (SGAs) are also used frequently, followed by the stimulants and non-stimulants (modafinil). Polypharmacy, defined as taking at least two medications of a single class or multiple medications from different classes, was reported in nearly half of those patients receiving psychotropic medications, and this increases the potential for drug-drug interactions and risk of adverse effects.

The PATH (Paving the Way for Advancements in Treatment and Health) for PWS Study

Started by FPWR in 2015, the PATH for PWS Study is a four-year, prospective, noninterventional observational study to advance the understanding of serious medical events in PWS. Every six months, participants complete a questionnaire regarding many health items including a medication list and serious medical events. There have been 647 respondents, and data collection has continued although recruitment has been closed. Ages at enrollment were 5–11 years (n = 218), 33.7%; 12–17 years (n = 177), 27.4%; and 18+ years (n = 252), 38.9%. Participants were from four countries: 88.6% from the USA, 7.7% Canada, 2.8% Australia, and 0.9% New Zealand. There has been a high retention rate of 93%. Data includes the age at which medications were started, the dosage, the frequency, and the level of benefit, whether ongoing or stopped, and if stopped, the age and reason are specified. In the spring of 2021, all psychotropic medications were pulled for analysis. In the 5–11 years age group, 33.6% were receiving psychotropic medi-

Table 22.7 Scattergram indicating the distribution of three psychotropic medications among 13.9% of NIH PWS Registrants' clinic contacts

SSRI	SNRI	Other	AHD	SGA	FGA	ACH	AED	Li	MPH	AMP	NStim	MOD	MEL	NAL
				x			xx							
xx		x												
x				x						x				
xx									x					
				xxx										
x							x		x					
x				x			x							
xx												x		
x			x				x							
x			x										x	
x				x	x									
x							xx							
				x			x					x		
x							xx							
			x						x			x		
				x		x	x							
x						x			x					
			x				x						x	
xx				x										
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xx				x										
x				x			x							
			x	x									x	
x					x		x							
x							x					x		
x			x				x							
x			x				x							
			x	x				x						
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x				x							x			
				xx		x								
			x	x			x							

Key: *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitor, *Other* other antidepressant, *AHD* anxiety hypnotic drug, *SGA* second-generation antipsychotic, *FGA* first-generation antipsychotic, *ACH* anticholinergic agent, *AED* anti-epilepsy drug, *Li* lithium, *MPH* methylphenidate derivative, *AMP* amphetamine derivative, *NStim* non-stimulant, *MOD* modafinil, *MEL* melatonin, *NAL* naltrexone

Table 22.8 Scattergram indicating the distribution of four psychotropic medications among 6% of NIH PWS Registrants' clinic contacts

SSRI	SNRI	Other	AHD	SGA	FGA	ACH	AED	Li	MPH	AMP	NStim	MOD	MEL	NAL
			x	xx			x							
x				x		x	x							
	x	x					x		x					
x			x	xx										
			x	x					x				x	
			x	x					x				x	
x				x			x					x		
x					x		xx							
x							xx	x						
x						x			x		x			
xx				x							x			
x			x	x									x	
x			x	xx										
x				xx			x							
x			x						xx					
x				xx									x	
x			x				x					x		
x				x			x	x						
xxx				x										
x				x	x		x							

Key: *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitor, *Other* other antidepressant, *AHD* anxiety hypnotic drug, *SGA* second-generation antipsychotic, *FGA* first-generation antipsychotic, *ACH* anticholinergic agent, *AED* anti-epilepsy drug, *Li* lithium, *MPH* methylphenidate derivative, *AMP* amphetamine derivative, *NStim* non-stimulant, *MOD* modafinil, *MEL* melatonin, *NAL* naltrexone

Table 22.9 Scattergram indicating the distribution of five psychotropic medications among 3% of NIH PWS Registrants' clinic contacts

SSRI	SNRI	Other	AHD	SGA	FGA	ACH	AED	Li	MPH	AMP	NStim	MOD	MEL	NAL
x			x	xx									x	
xx		x		x					x					
x			x	x					x				x	
x	x	x		xx										
x					x		xx	x						
x			xx		x		x							
			x	x			x		xx					
x			x						x			x	x	
x				xx			x		x					
x				xx			x					x		

Key: *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitor, *Other* other antidepressant, *AHD* anxiety hypnotic drug, *SGA* second-generation antipsychotic, *FGA* first-generation antipsychotic, *ACH* anticholinergic agent, *AED* anti-epilepsy drug, *Li* lithium, *MPH* methylphenidate derivative, *AMP* amphetamine derivative, *NStim* non-stimulant, *MOD* modafinil, *MEL* melatonin, *NAL* naltrexone

Table 22.10 Scattergram indicating the distribution of six psychotropic medications for 0.6% of NIH PWS Registrants' clinic contacts

SSRI	SNRI	Other	AHD	SGA	FGA	ACH	AED	Li	MPH	AMP	NStim	MOD	MEL	NAL
			x	xx	x		xx							
x	x	x	x	x										x

Key: *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitor, *Other* other antidepressant, *AHD* anxiety hypnotic drug, *SGA* second-generation antipsychotic, *FGA* first-generation antipsychotic, *ACH* anticholinergic agent, *AED* anti-epilepsy drug, *Li* lithium, *MPH* methylphenidate derivative, *AMP* amphetamine derivative, *NStim* non-stimulant, *MOD* modafinil, *MEL* melatonin, *NAL* naltrexone

Table 22.11 Scattergram indicating the distribution of seven psychotropic medications among 1.5% of NIH PWS Registrants' clinic contacts

SSRI	SNRI	Other	AHD	SGA	FGA	ACH	AED	Li	MPH	AMP	NStim	MOD	MEL	NAL
			x	xx		x	xx		x					
x	x				xx		x		x	x				
x			x			x	x		x	x			x	
xx				x					x	x		x	x	
xx			x	x					x	x	x			

Key: *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitor, *Other* other antidepressant, *AHD* anxiety hypnotic drug, *SGA* second-generation antipsychotic, *FGA* first-generation antipsychotic, *ACH* anticholinergic agent, *AED* anti-epilepsy drug, *Li* lithium, *MPH* methylphenidate derivative, *AMP* amphetamine derivative, *NStim* non-stimulant, *MOD* modafinil, *MEL* melatonin, *NAL* naltrexone

Table 22.12 Scattergram indicating the distribution of eight psychotropic medications among 0.3% of NIH PWS Registrants' clinic contacts

SSRI	SNRI	Other	AHD	SGA	FGA	ACH	AED	Li	MPH	AMP	NStim	MOD	MEL	NAL
xx		x		xx		x	x						x	

Key: *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitor, *Other* other antidepressant, *AHD* anxiety hypnotic drug, *SGA* second-generation antipsychotic, *FGA* first-generation antipsychotic, *ACH* anticholinergic agent, *AED* anti-epilepsy drug, *Li* lithium, *MPH* methylphenidate derivative, *AMP* amphetamine derivative, *NStim* non-stimulant, *MOD* modafinil, *MEL* melatonin, *NAL* naltrexone

Table 22.13 Scattergram indicating the distribution of nine psychotropic medications for 0.3% of NIH PWS Registrants' clinic contacts

SSRI	SNRI	Other	AHD	SGA	FGA	ACH	AED	Li	MPH	AMP	NStim	MOD	MEL	NAL
xxx		x	x	xx			x		x					

Key: *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitor, *Other* other antidepressant, *AHD* anxiety hypnotic drug, *SGA* second-generation antipsychotic, *FGA* first-generation antipsychotic, *ACH* anticholinergic agent, *AED* anti-epilepsy drug, *Li* lithium, *MPH* methylphenidate derivative, *AMP* amphetamine derivative, *NStim* non-stimulant, *MOD* modafinil, *MEL* melatonin, *NAL* naltrexone

cations. In the 12–17 years age group, 49.1% were receiving psychotropic medications. In the 18+ years age group, 65.5% were receiving psychotropic medications. In the PATH Study, the use of all psychotropic drug classes increased with age. Table 22.14 identifies the classes and generic names of medications; this is not an all-inclusive list of medications used by the participants in the PATH Study.

Figure 22.4 identifies the psychotropic medications by class used within each age group in the PATH Study [88].

The distribution of medications by age group demonstrates the degree of polypharmacy with age in the PATH Study (Fig. 22.5) [88]. Clearly, polypharmacy increases with age.

The data from the PATH Study and the PWS Registry are challenging to compare for several reasons. First, these PATH data are based on prevalence, while the PWS Registry has recorded the age at which medication was started. Second, the age group clusters differ. Third, the classification of medications is not the same. Finally, the start-up dates of recruitment differ by almost a decade. The frequency of polypharmacy was analyzed by age cohort in the PATH Study; this did not occur in PWS Registry data. Nonetheless, Table 22.15 compares the percentage of each age group receiving psychotropic medication by drug class.

It is important to note that the PATH Study was started a decade after the PWS Registry. Over these ten years, there have been some interesting changes in prescribing trends. First, the age of use of antidepressant medication, specifically SSRIs, has been shifted to the late adoles-

Table 22.14 Classification system for psychotropic medications used in the PATH Study

Alertness/ ADHD	• Amphetamine • Concerta • Dexmethylphenidate	• Dextroamphetamine • Guanfacine • Lisdexamfetamine	• Methylphenidate • Modafanil • Pitolisant	• Provigil • Ritalin
Anti-Anxiety	• Buspirone			
Anti-Depressants	**SNRI Anti-Depressant** • Atomoxetine • Desvenlafaxine • Duloxetine	• Levomilnacipran • Milnaciparan • Venlafaxine	**SSRI Anti-Depressant** • Citolopram • Escitalopram • Fluoxetine • Fluvoxamine	• Paroxetine • Sertraline • Trazodone • Vortioxetine
	Other Anti-Depressant • Amitriptyline • Bupropion • Bupropion Hydrochoride • Clomipramine	• Imipramine • Mirtazapine • Naltrexone • Nortriptylin		
Antipsychotics	**Atypical Antipsychotic** • Aripiprazole • Asenapine • Brexpiprazole • Cariprazine	• Clozapine • Iloperidone • Lurasidone • Olanzapine	• Paliperidone • Quetiapine • Risperidone • Seroquel	• Sertindone • Ziprasidone • Zotepine
	Other Antipsychotic • Chlorpromazine • Haloperidol • Perphanazine • Thioridazine			
Mood Stabilizer	• Carbazepine • Divalproex • Gabapentin • Lamotrigine	• Lithium • Nuedexta • Oxcarbazepine • Oxytocin	• Sodium valproate • Tiagabine • Topiramate • Valproic Acid	• Zonisamide
Sedative Hypnotic	• Aprozalam • Clonazepam • Clonidine • Cyproheptadine • Estazolam	• Eszopiclone • Hydroxyzine • Lorazepam • Prazosin • Propranolol	• Ramelteon • Sodium oxybate • Suvorexant • Temazepam • Triazolam	• Valium • Xanax • Zaleplon • Zolpidem

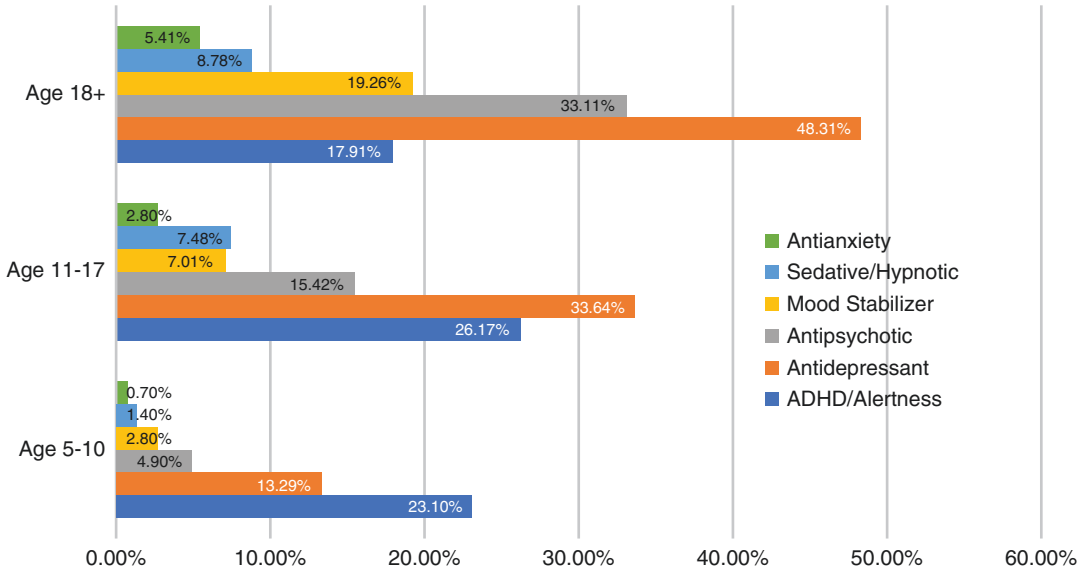

Fig. 22.4 Percent utilization of each class of psychotropic medication per age group

cent and young adult years. Similarly, there is a shift in the use of antipsychotics and mood stabilizers to later years. Second, the use of stimulants is similar in the youngest cohort of both data bases but decreases markedly with age in the PWS Registry. Third, the use of antipsychotic medication and mood stabilizers increases with age in both data bases but is higher among all age cohorts in the PWS Registry. Both data sets indicate that the use of antidepressants, antipsychotics, and mood stabilizers increases with age, increasing the potential for multiple medications

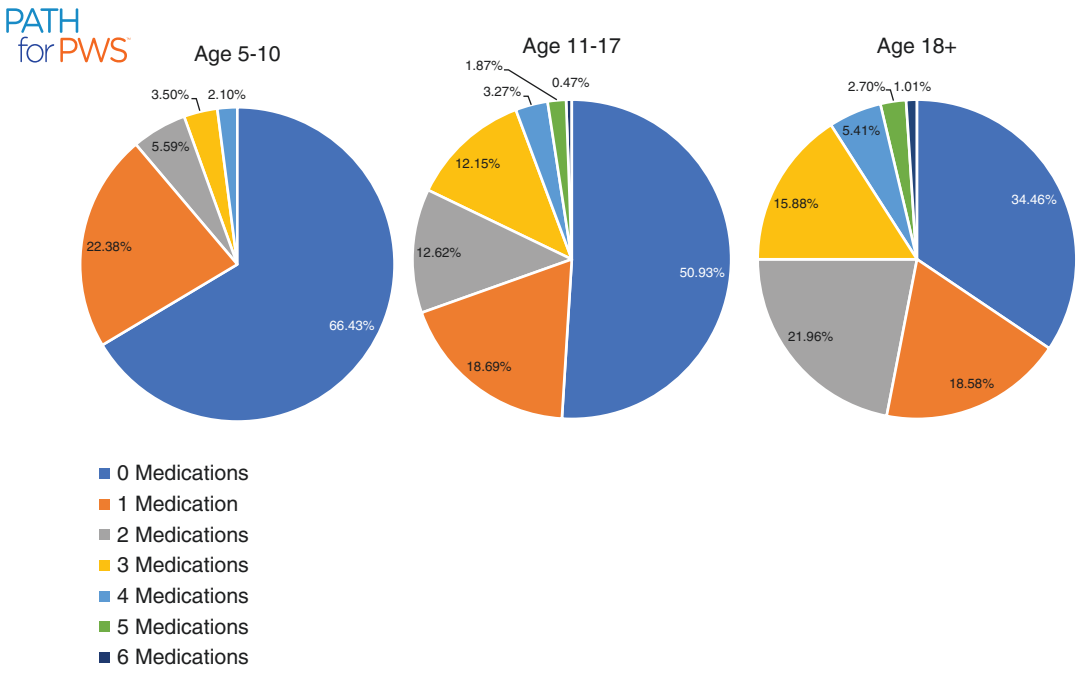

Fig. 22.5 Polypharmacy of psychotropic medications by age group

Table 22.15 Percentage of each age group receiving psychotropic medication by drug class

	ADHD/wakefulness	Antidepressants	Antipsychotics	Mood stabilizers
PATH Study	23/26/18	13/34/48	5/15/33	3/7/19
PWS Registry	25/7/9	48/70/46	20/33/40	14/25/42

Age cohorts: PATH Study, 5–11/12–17/18+ years; PWS Registry, 5–<12/12–<21/>21 years

to be used concurrently. There is minimal evidence that polypharmacy improves treatment outcome, and it most certainly increases risk of adverse effects.

Efficacy of Psychotropic Medication

The Vanderbilt Study

In the Vanderbilt study, parents of 86 persons with PWS ages 8–51 years (mean age = 24 years) were asked to comment on whether they thought the SSRI or antipsychotic medication was helpful with typical behavioral symptoms associated with the phenotype. These anecdotal responses indicated that both SSRIs and antipsychotic medications influenced the irritability, compulsivity, and tantrums associated with PWS; food issues were not improved. These results are found in Table 22.16.

Table 22.16 Parental or care provider responses regarding the efficacy of SSRIs or antipsychotic medication in the Vanderbilt study

	SSRIs		Antipsychotics	
	No	Yes	No	Yes
Tantrums	14%	86%	4%	96%
Skin picking	60%	40%	47%	53%
Compulsions	29%	71%	37%	63%
Irritability	14%	86%	7%	93%
Food issues	61%	39%	72%	28%

Key: *SSRIs* selective serotonin reuptake inhibitors

The Bonnot Meta-Analysis

In the Bonnot meta-analysis from 2016, the authors considered the class of psychotropic medication, efficacy, and side effects among the selected studies [8]. Altogether, there were 102 patients described in the studies, as indicated in Table 22.17.

Across the studies reviewed, the authors concluded that topiramate was effective for skin picking and impulsive aggression, but effects on weight were inconsistent. Risperidone was effective for treating psychosis, but like other atypical antipsychotics, the side effect of weight gain was problematic; no other adverse effects were reported. N-acetylcysteine (NAC) was effective for the management of skin picking. Pharmacotherapy of hyperphagia was disappointing, although some studies suggested short-term improvement.

Other studies: Subsequent to the Bonnot meta-analysis, some single case reports were published. Briegel et al. reported that aripiprazole (5–7 mg/d) was used in a 16-year-old female for psychosis with recurrence of symptoms after dose reduction; a 2 kg weight gain was reported over 2 years [9]. East and Maroney reported success using aripiprazole (10 mg BID) and topiramate (100 mg BID) during a 30-day hospitalization for an 11-year-old African American male with PWS and ADHD who displayed aggressive behavior related to food acquisition [35]. Puri et al. used a combination of naltrexone and bupropion for the management of impulsivity and hyperphagia in an adolescent [113]. Singh reported that aggression was decreased with guanfacine extended release in an adolescent with PWS [126].

Also, several case series have been published. Singh et al. reported the results of a retrospective cohort of 27 patients with PWS, ages 6–26, receiving guanfacine extended release. He found that 9 patients showed improvement with skin picking, 14 patients showed improvement with agitation and aggression, 16 patients showed improvement with ADHD symptoms, and 2 patients with psychotic symptoms did not respond to guanfacine XR [127, 128]. Consoli et al. looked at the effects of topiramate vs placebo over 8 weeks on the behavioral manifestations of irritability/impulsivity, self-injury, and eating behavior in 30 persons with genetically confirmed PWS ages 12–45 years; they found that the dose (50–200 mg/day) and duration of treatment with topiramate were effective in modulating the eating behavior in PWS compared to those receiving placebo, but there was no significant effect on other behaviors except for an increase in lethargy [21]. Deest et al. implemented an open-label trial of sertraline in 14 patients with PWS for the management of temper tantrums and found that behaviors were improved at low doses (25 mg median, 25–100 mg range) over 6 months, and other classes of medication used for behavior management were decreased in some [25].

Table 22.17 Bonnot meta-analysis of efficacy of 102 patients receiving psychotropic medications

Medication	Doses	Number of studies	Number of patients	Trial duration	Target symptoms
Risperidone		3	11		Psychosis
Fluoxetine[a]		5	6	6 months	"OCD," SIB, hyperphagia
Naltrexone		2	2		SIB, obesity
Topiramate		2	16	8 weeks	SIB, impulse/aggression, weight stabilized in 7/16
Fluvoxamine		1	1		"OCD"
N-acetylcysteine	900 mg	1	35		Skin picking
Mazindol[b]	1–2 mg	1	2	24 weeks	Hyperphagia
Rimonabant	20 mg	1	15		Hyperphagia
Fenfluramine		1	15		Hyperphagia

[a]Two women developed menses after taking fluoxetine for six months
[b]Mazindol is a sympathomimetic used for weight loss
Key: OCD obsessive compulsive disorder, *SIB* self-injurious behavior

Pharmacogenetics, Pharmacokinetics, and Pharmacodynamics Affecting Medication Response in PWS

Pharmacogenetics

Cytochrome P450 enzymes (CYPs) are responsible for catalyzing the oxidative metabolism and elimination of 75% of xenobiotics, endogenous steroids, and drugs through the liver [112]. Some are also required for metabolism of prodrugs to the active metabolite, such as conversion of venlafaxine to desvenlafaxine. Of all psychotropic medications, the majority are metabolized through six of the enzymes in the cytochrome P450 system: CYP2D6, CYP2B6, CYP2C19, CYP2C9, CYP3A4, and CYP1A2. Some exceptions are lithium, gabapentin, lamotrigine, and lorazepam. The Flockhart table displays the cytochrome P450 enzymes and their substrates, inducers, and inhibitors; it can be found online at http://drug-interactions.medicine.iu.edu [40]. A similar table with discussion of relevance to PWS has been published [43]. There is a growing trend toward personalized medicine, which includes genetic testing of cytochrome P450 enzymes to ascertain the metabolic profile for medication use in each person to optimize therapeutic outcome.

Polymorphisms of the genes that encode these cytochrome P450 enzymes may produce different metabolic phenotypes that have ethnic and gender specificity [95, 96]. The metabolic phenotypes are characterized as ultrarapid, extensive (normal), intermediate, or poor metabolizing. These metabolic phenotypes determine serum drug levels, therapeutic response, or adverse effects [149]. Pharmacogenetic testing examines each person's DNA, reports the polymorphisms for each cytochrome, identifies a metabolic phenotype, and informs medication selection and dose determination [69]. These gene polymorphisms are inherited from the parents; a family history of medication sensitivity and therapeutic response may inform potential differences in drug metabolism. A poor or intermediate metabolizer may require lower starting doses of medication and slower dose titration than recommended in the Physicians' Desk Reference (PDR) to achieve therapeutic levels. At standard doses of medication, toxicity may occur resulting in adverse effects. On the other hand, an ultrarapid metabolizer may require higher doses of medication to achieve therapeutic levels and may require a more frequent dosing schedule through the day due to unwanted withdrawal symptoms, also related to the occurrence of adverse effects.

In a case series of 35 patients with PWS (14 DEL (deletion), 16 UPD, and 5 methylation positive but subtype undetermined) who received pharmacogenetic testing, there were polymorphisms in *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP3A4*, and *CYP1A2* leading to phenotypic differences among PWS genetic subtypes, potentially affecting drugs metabolized by these cytochromes [43]. These patients were referred to regional centers for evaluation and treatment, and they received pharmacogenetic testing at part of their medical care because, most likely, they had failed previous pharmacological interventions. Although larger studies in a non-referred population are required to validate these results, they do tend to validate findings that some individuals with PWS are more sensitive to medications and may experience adverse reactions, such as mood and behavioral activation, without careful dose modulation. Some pertinent findings are discussed.

Cytochrome 2D6 is responsible for the oxidative metabolism of many psychotropic medications including antidepressants, atypical antipsychotics (SGAs), stimulants, and nonstimulants that are used in PWS. Overall, more than half of the patients in the case series had slower metabolism than expected. Among the deletion (DEL) subtypes compared to a normative population, there were fewer extensive metabolizers and more intermediate and poor metabolizers; those with UPD had more poor metabolizers only. This group data suggests that greater vigilance is required for selection and dosing of medications primarily metabolized by CYP2D6, such as fluoxetine, risperidone, sertraline, aripiprazole, citalopram, escitalopram, paroxetine, bupropion, amphetamine, clonidine, and ziprasidone.

Cytochrome 2C19 is responsible for metabolism of many antidepressants, gonadal steroids, and proton pump inhibitors. Compared to a normative population, there were more ultrarapid metabolizers among DEL and more extensive metabolizers among UPDs that may affect dose selection and monitoring for fluoxetine, sertraline, citalopram, and escitalopram. Because CYP2C19 metabolizes estradiol, progesterone, and testosterone, the dosing pattern of these SSRIs will be affected through competitive action at binding sites.

Cytochrome 2C9 is responsible for metabolism of fluoxetine, sertraline, and valproate. Compared to a normative population and patients with DEL, those with UPD had fewer extensive metabolizers and more intermediate and poor metabolizers.

Cytochrome 3A4 metabolic phenotype among DEL and UPDs is decreased compared to normative populations. This has specific relevance to PWS because it is affected by growth hormone in a gender-specific way [131]. Sinues et al. found that in growth hormone deficient children, substitutive therapy lowered CYP3A4 activity selectively in males. Although CYP3A4 metabolizes 60% of medications [112], it has primary affinity for aripiprazole, benztropine, cannabidiol, mirtazapine, quetiapine, trazodone, and ziprasidone only, and these medications are most likely to be affected by concurrent treatment with growth hormone.

CYP1A2 is most interesting for PWS because the gene is located at Ch 15q24.1, just outside the PWS critical region. In the PWS case series, there were more ultrarapid metabolizers, especially among UPDs, and they were no poor metabolizers. Further, there was more duplication of alleles and complex genotypes among UPDs compared to DEL and typical population. It is possible that the patient with maternal uniparental disomy 15 may have two identical CYP1A2 alleles, especially because two-thirds of all UPDs have segmental or total isodisomy [12]. CYP1A2 is unique among the cytochromes because of its inducibility by tobacco smoke, caffeine, insulin, modafinil, nafcillin, omeprazole, and/or cruciferous vegetables. In the presence of the hyper-inducible allele, the phenotype is converted from extensive to ultrarapid metabolizer status. For example, there is a three- to fivefold increase in CYP1A2 activity in the presence of cigarette smoking [155]. Persons with PWS are likely to follow some version of the Red Yellow Green diet that contains a high proportion of cruciferous vegetables (Brussels sprouts, broccoli, cauliflower, cabbage, radish, rocket, water cress, and wasabi), which will result in hyper-induction with an increase as much as 25% [155]. As a result, the metabolism of fluvoxamine, haloperidol, melatonin, olanzapine, thioridazine, chlorpromazine, and imipramine is likely to be affected. CYP1A2 activity has gender specificity also, with higher metabolic activity in men than women. Estradiol, oral contraceptives, and some antibiotics (ciprofloxacin and levofloxacin) are inhibitors of CYP1A2, which may alter the therapeutic effects of medications prescribed for psychiatric conditions resulting in toxicity. Because CYP1A2 eliminates environmental toxins such as heterocyclic amines and polycyclic hydrocarbons, polymorphisms have been investigated in certain malignancies, such as cancer of the bladder, colon, and rectum.

Factors Affecting Pharmacokinetics in PWS

Pharmacokinetics is a field of study directed toward understanding the fate of a drug once it enters the body. It involves activation, distribution, bioavailability, and elimination. The mode of entry of a drug is important in PWS. Although most medications are administered orally, there are notable exceptions. Growth hormone is given by injection; testosterone is given by injection or gel; estradiol may be administered as a patch or given orally; and progesterone may be administered intradermally as a time release agent. Oxytocin can be administered as an intranasal spray [62]. There are a few long-acting antipsychotic drugs that are injected into the muscle. Oral medications enter the system through the gastrointestinal tract, while topical or injected agents enter the bloodstream directly through the

skin or the muscle. The major factors affecting absorption from the GI tract in PWS are delayed gastric emptying and constipation that promotes enteric reabsorption. Stomach acidity may affect absorption, especially for amphetamines except Vyvanse [82]. For most medications, the liver is a major transportation hub for activation, protein binding, and/or elimination. Liver size and activity are higher in young children before puberty and result in increased drug metabolism that may require multiple daily dosing [90]. Also, nutrition and disease states, such as fatty liver, affect enzyme metabolism [80]. The bioavailability of a drug is determined by the amount of active metabolite in the blood that is distributed to the desired organ system. In young children, protein binding is decreased, and drug availability in the bloodstream is increased, which may lead to increased risk of side effects [90]. The volume of distribution of a drug is affected by the systemic circulation and body composition (lean body vs fat mass). Lipophilic drugs are more likely to accumulate in the adipose tissue, decreasing bioavailability and delaying clearance through the liver. If the endpoint of distribution is the brain, the drug must cross the blood-brain barrier, and there are specific genetic polymorphisms that affect this membrane transit. Most medications are metabolized by the liver and excreted in feces and urine. Urine pH may affect excretion, especially with amphetamines [82]. Glomerular filtration rate is increased in young children resulting in faster urinary excretion [90]. Some medications, like lithium and gabapentin, are eliminated unchanged through the kidneys.

Pharmacodynamic Factors Affecting Medication Response in PWS

Once a drug reaches the brain, there are neurotransporters and neurotransmitters that determine the effect of the psychiatric medication on the person. There are individual variations in medication response that are determined by polymorphisms of pharmacodynamic genes such as serotonin transporter, serotonin 2A and 2C receptors, catechol-o-methyltransferase, adrenergic receptor 2A, and methylene tetrahydrofolate reductase.

In the case series of 33 patients with PWS (14 DEL, 14 UPD, and 5 PWS unspecified, methylation positive, and subtype undetermined), pharmacodynamic testing was performed as part of the clinical evaluation. These patients were referred to regional centers because of untoward response to previous medication trials or comorbidity likely to require more than one psychotropic medication. The results of pharmacodynamic testing in this patient cohort revealed polymorphisms with PWS subtype differences in all genes tested [42]. The results from serotonin transporter, serotonin receptors, adrenergic receptor 2A, and methylene tetrahydrofolate reductase will be discussed highlighting their contribution to pharmacotherapy in PWS. Further, polymorphisms of catechol-o-methyltransferase in PWS appear to contribute to our understanding of phenotypic behaviors and psychiatric comorbidity.

The serotonin transporter is the site of action of SSRI medications. Two polymorphisms in the promoter site of the gene, *SLC6A4*, have been studied the most, because they predict medication response. The short allele (s) is associated with stress sensitivity and decreased medication response to SSRIs, and the long allele (L) is associated with resilience and increased sensitivity to SSRIs. The distribution in the normative population is skewed toward the L/L, with the most common allelic combination s/L [111]. Among the PWS UPD cohorts, the L allele frequency was 0.77 compared to 0.60 among Caucasian Americans and 0.41 among DEL. Among the DEL cohorts, the s allele frequency was 0.59 compared to 0.40 among Caucasian Americans and 0.23 among UPDs. These data suggest that patients with UPD are more likely to respond to SSRIs and may demonstrate a greater tendency toward mood activation, while patients with DEL may be less responsive and demonstrate more traits of stress sensitivity, neuroticism, and somatization.

There are two serotonin receptors that are key to medication response for SSRIs and atypical neuroleptics: serotonin 2A (HTR2A) and sero-

tonin 2C (HRT2C). They are G-coupled receptors that are developmentally regulated and have an opposing action in the prefrontal cortex (PFC) of the brain. Serotonin 2A receptors are located on excitatory glutamate neurons, and serotonin 2C receptors are located on inhibitory GABA interneurons [75]. During the developmental period, HRT2A mRNA is expressed at greater levels than HRT2C, resulting in a tendency toward activation. Further, in PWS, there is faulty editing of HRT2C that may result in deficient inhibitory function. With SSRI treatment, the net effect is activation that may lead to mood and behavioral change. This difference in mRNA expression reaches parity in early adulthood. This may be the neurochemical underpinning of the phenomenon of mood and behavioral activation in children and adolescents that has resulted in the black box warning for suicide potential when starting on SSRIs. Further support for this hypothesis comes from post suicide analysis of victims' PFC and ACC where alternative RNA editing of HRT2C produced isoforms with reduced function [151].

The frequency of HRT2A polymorphisms was tested in the referred cohort of PWS patients and compared to individuals of European ancestry. Compared to the results from the UPD group and the normative populations, patients with DEL had an increased frequency of the low activity phenotype that predicts a greater risk for adverse effects with the use of SSRIs.

Alpha-2A-adrenergic receptor (ADRA2A) is a G-coupled receptor that provides presynaptic feedback inhibition on norepinephrine release from sympathetic neurons that modulate vascular reactivity to stress and medication response of alpha-adrenergic agonists and methylphenidate in the treatment of ADHD. Testing results in the referred patient cohort indicate that the DEL group had a higher frequency of alleles conferring increased medication response, while the UPD group had the opposite.

Methylene tetrahydrofolate reductase (MTHFR) is an enzyme in the gut that converts dietary folate into the biologically active form, L-methyl folate, which catalyzes brain energy processes and drives the methylation cycle responsible for the synthesis of the monoamine neurotransmitters. A low functioning enzyme results in oxidative stress that contributes to a variety of medical and neuropsychiatric illnesses [48]. The most common cause for MTHFR deficiency is familial transmission of polymorphisms with diminished function. The most studied single nucleotide polymorphisms (SNPs) of MTHFR are 677C > T and the 1298A > C, both of which result in a proportional decrease in enzyme function across allelic frequencies. Among the referred cohorts of patients with PWS, over half were heterozygotes of 677C > T, exceeding values in a normative Caucasian population. Of interest, there were more wild-type polymorphisms 677C > T among those with UPD compared to those with DEL.

MTHFR deficiency has been associated with stress-induced depression, major depressive disorder, bipolar disorder, and schizophrenia [68, 81, 106]. Low serum folate has been associated with treatment-resistant depression [91]. Currently, supplementation with L-methyl folate is an accepted clinical strategy for managing treatment-resistant depression [67], where 15 mg/day is more effective than 7.5 mg/day [103, 145]. Because mood stabilizers, such as lithium, valproic acid, and lamotrigine, may interfere with MTHFR activity, supplementation with L-methyl folate is recommended [5]. Given the prevalence of mood and psychotic disorders in PWS, and the use of AED/mood stabilizers, L-methyl folate supplementation should be considered.

Adverse Effects of Psychotropic Medications

Currently, there are no systematic studies in the literature examining adverse effects among patients with PWS receiving psychotropic medications. However, there are some case reports. There are two reports involving fluoxetine for failure to modify skin picking [120] and for aggravating food-related behavior [73]. There is one report of psychosis associated with fluoxetine use [59]. In the state chapter pilot study

assessing medication utilization data from 27 families who had a child with PWS ages 6–49 (mean age 22 years), 44% of parents or caregivers reported adverse effects to medications, most commonly weight gain, motor restlessness, and sedation, while 56% reported that some medications had been discontinued because they were ineffective or were no longer effective (see section "PWSA State Chapter Survey").

Drug-Drug Interactions

Adverse events and treatment failures are due often to drug-drug interactions. The enzymes of the cytochrome system rarely metabolize just one medication, so the potential exists for competitive metabolism. Medications can also act as inhibitors or inducers of cytochromes as described in the Flockhart table [40]. Polypharmacy is likely to increase the potential for drug-drug interactions.

Phenoconversion occurs when the metabolic phenotype of a cytochrome is changed to another because of the action of a drug, a nutraceutical/dietary supplement, an endogenous process, or an environmental factor [71]. An extensive or intermediate metabolizer of CYP2D6 can be phenoconverted to a poor metabolizer in the presence of bupropion, fluoxetine, and paroxetine, which are CYP2D6 inhibitors, resulting in toxicity for a person receiving risperidone or aripiprazole [95, 96]. Vitamin D induces *CYP3A4* transcription resulting in increased phenotypic activity of CYP3A4, which increases turnover of vitamin D metabolites resulting in vitamin deficiency and bone loss. Endogenous processes such as inflammation may shift downward the metabolizing status of cytochromes 2C9, 2C19, 2D6, and 3A4 (Klomp et al.). Diseases of the liver may impair metabolism at any age. For example, steatohepatitis (fatty liver) selectively decreased CYP2C19 function by 89% [80]. Finally, the activity of cytochromes 1A2, 2C9, 2C19, and 2D6 is increased by obesity among children, while activity of CYP1A2 and CYP3A4 is decreased in adults with obesity [80].

Herbal- or plant-based agents may interact with prescribed medications, such as St. John's wort, which inhibits CYP1A2, CYP2C9, and CYP3A4, resulting in toxicity of clomipramine, a substrate for all three cytochromes. Both cannabis and cannabidiol are substrates for CYP2C19 and CYP3A4 and inhibit CYP2D6 and CYP2C9. When used together with fluoxetine, mood and behavioral activation may occur. Because all these agents have a relatively long half-life, it may take a while for adverse symptoms to present and similarly long time for them to diminish after discontinuation. It is strongly advised to consult the Flockhart table before adding a new medication to an existing regimen, especially considering the frequency of polypharmacy among patients with PWS.

Black Box Warnings for Suicide Risk and Cardiac Dysfunction

Black box warnings are issued by the FDA when sufficient concern for morbidity and potential mortality is associated with a specific medication or dose of medication. These guidelines are not so severe that the medication must be removed from the market, although this has occurred in the past with the stimulant Cylert (pemoline) or the SNRI Serzone (nefazodone), which were associated with chemical hepatitis, and most recently with the proton pump inhibitor, Zantac (ranitidine), that was suspected of carcinogenesis. Black box warnings have been issued for the use of SSRIs and SNRIs in children and adolescents due to the risk of mood activation with suicide risk. Warnings have also been issued for citalopram at doses greater than 40 mg/day due to risk of QTc lengthening on the electrocardiogram (see Fig. 22.6), which might also occur with the following antipsychotics: haloperidol, paliperidone, iloperidone, pimozide, quetiapine, asenapine, ziprasidone, and thioridazine. Tricyclic antidepressants are known to lengthen PR interval and QTc in a dose-related manner (see Fig. 22.4). These electrical changes predispose to conduction blockade and cardiac arrhythmias [154]. These warnings indicate the

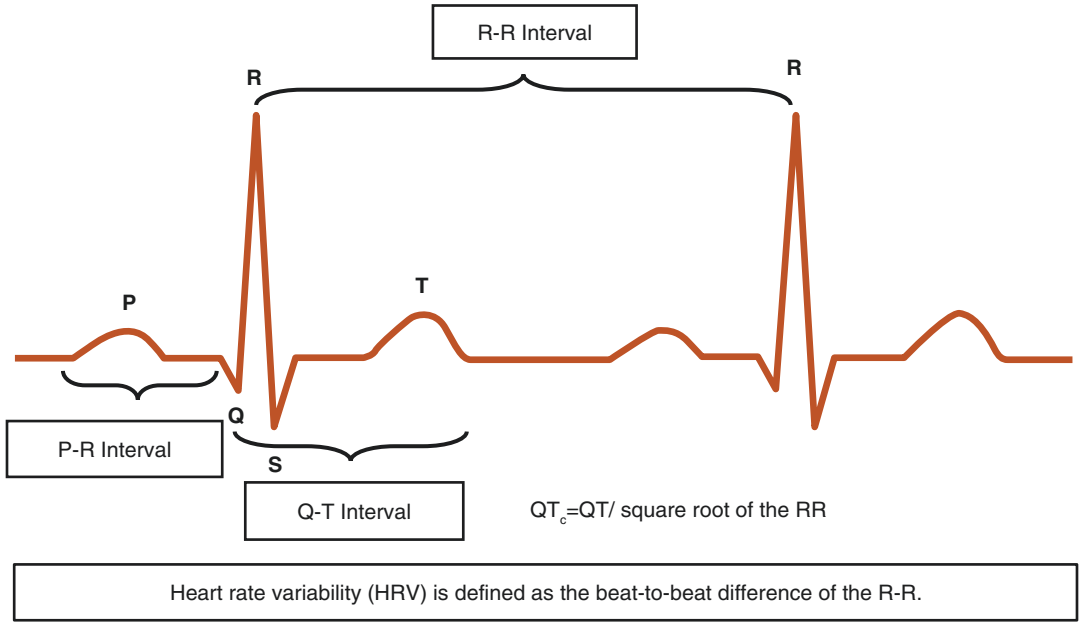

Fig. 22.6 Parameters measured on an electrocardiogram

need for greater surveillance and risk management when using these agents. Obtaining a baseline ECG and rechecking parameters during dose titration are recommended.

Mood and Behavioral Activation

In 2006, mood and behavioral activation in a case series was reported [97]. In 2007, Forster and Gourash presented findings of iatrogenic mood and behavioral activation (MBA) in patients with PWS predominantly due to SSRI medication [44]. The relative frequency of agents associated with MBA can be found in Fig. 22.7.

In 2008, Harada et al. published criteria for mood and behavioral activation in typical patients receiving SSRIs. Patients were classified as developing the activation syndrome if they experienced any symptom of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania [56]. They suggested that MBA was related to the dose of SSRI, and depending on the severity of symptoms, a dose reduction managed the syndrome. In conclusion, treatment with

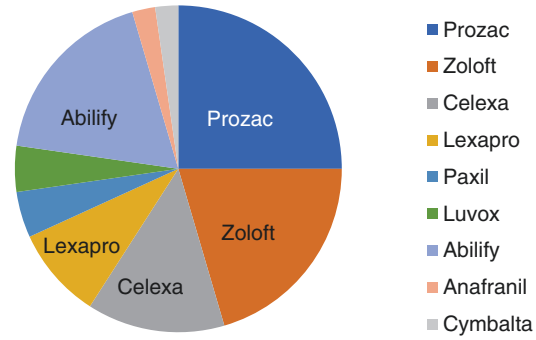

Fig. 22.7 Psychotropic medications associated with mood and behavioral activation. Key: Prozac (fluoxetine), Zoloft (sertraline), Celexa (citalopram), Lexapro (escitalopram), Paxil (paroxetine), Luvox (fluvoxamine), Abilify (aripiprazole), Anafranil (clomipramine), Cymbalta (duloxetine)

high-dose SSRIs carries a risk for MBA in all populations at all ages.

In a retrospective review of clinical cases, 25 individuals with PWS (9 UPD, 9 DEL, 6 genetic subtype undetermined, 1 atypical), ages 11–27 years, displayed symptoms of mood and behavioral activation [30]. The doses at which MBA occurred were determined to be the typical starting doses of medication recommended in the

PDR (fluoxetine equivalent = 5 mg), as described in Table 22.18 [30].

There were temporal parameters associated with mood and behavioral change as noted in Fig. 22.8 as adapted from [51].

This gradual change may reflect mechanisms and time course of neurotransmitter action. Because serotonin receptors are G-protein coupled and work through second messengers that involve transcription factors, it takes 4–6 weeks to experience the full effects (or adverse effects) of dosing changes when administering SSRIs.

Table 22.18 Typical starting doses, maximum doses, and doses above which mood and behavioral activation occurred in persons with PWS

Agent	Typical starting dose	Typical maximum dose	PWS activating dose
Prozac (fluoxetine)	10–20 mg	80 mg	10 mg
Zoloft (sertraline)	25 mg	200 mg	25 mg
Celexa (citalopram)	10 mg	40 mg	5 mg
Lexapro (escitalopram)	10 mg	20 mg	5 mg
Paxil (paroxetine)	10 mg	50 mg	+
Luvox (fluvoxamine)	25 mg	300 mg	25 mg
Anafranil (clomipramine)	25 mg	200 mg	+
Cymbalta (duloxetine)	20 mg	120 mg	+
Abilify (aripiprazole)	2–2.5 mg	30 mg	2.5 mg

[a]Data absent

In the case series, symptoms of mood and behavioral activation were managed by gradual dose reduction and discontinuation of the activating agent. Although the symptoms of MBA diminished, very few individuals remained medication free. Most individuals (23/25) went onto required mood stabilizers and/or atypical antipsychotic medication to manage mood and behavioral symptoms. In several cases, withdrawal emergent depressive symptoms were successfully treated with low doses of SSRI medication (equivalent of fluoxetine 5 mg or citalopram 10 mg). Neither age, gender, nor PWS genetic subtype predicted mood activation, withdrawal emergent effects, or ongoing mood instability.

Typical doses of SSRIs have a direct action on serotonin receptors and transporter resulting in an increase in serotonin in the synaptic cleft. SSRIs also bind to specific serotonin receptors on GABA and glutamate interneurons, affecting the balance between excitation and inhibition in the central nervous system. Serotonin 2A receptor (HTR2A) is expressed in excitatory interneurons (glutamatergic); HTR2C is expressed in inhibitory interneurons (GABAergic). Further, there is a decrease in GABA tone in PWS that results in inadequate inhibitory feedback that may contribute to MBA. Typical doses of SSRIs may precipitate MBA in PWS due to the disequilibrium of serotonin receptor effects on already diminished inhibitory GABA action. This is a serious and preventable iatrogenic disorder. Clinical experience suggests that MBA is managed by reducing the dose of SSRI, blocking excitatory serotonin

Observed Signs of Mood and Behavioral Activation

Early:
Increased intensity of typical behaviors in PWS such as perseveration, food seeking, irritability, tantrums, skin picking, including rectal picking.

Late:
Impulsive risk taking, self-injury, aggressive or disruptive behavior that is out of character for the person, i.e., threatening to stab self or others with scissors; repeatedly inserting fingers into a hornet nest to be stung, or inducing paper cuts; jumping out of a window, moving vehicle, or over a railing; grabbing the driver's wheel or gear shift while the car is in motion; impulsive ingestion of light bulbs, small toys, keys; self-biting, gouging, vaginal or rectal insertions; delusional thinking with sexual manifestations including false allegations of abuse.

Fig. 22.8 Temporal parameters associated with mood and behavioral activation in PWS

receptor (HTR2A) with an atypical neuroleptic (second-generation antipsychotic), and/or initiating treatment with GABA agonists, such as an anticonvulsant or lithium. Careful selection of atypical neuroleptic is necessary, because some, like aripiprazole, is a partial agonist of serotonin receptors.

During the developmental period, the brain is more sensitive to typical doses of SSRIs, and as a result, mood and behavioral activation is more likely to occur. The use of antidepressants in children and adolescents carries a black box warning. A proposed mechanism for mood and behavioral activation can be related to the age of the individual. During the developmental years, transcription of mRNA for the inhibitory 5HT2C serotonin receptor lags behind the transcription of the activating 5HT2A in the prefrontal cortex; this difference equalizes briefly in young adulthood but does not persist into adulthood [75]. As a result, serotonin receptors HTR2A and HTR2C come "online" at different times, as measured in postmortem studies by normalized mRNA expression in the human prefrontal cortex. During the developmental period, recommended starting doses of SSRIs can cause mood and behavioral activation due to an imbalance of availability of HTR2A (activating) and >HTR2C (inhibitory) serotonin receptors, whose timing of expression has a peak disparity occurring in adolescence. In neurotypical individuals, there is a bias toward activation. In PWS, abnormal editing of HTR2C receptors may lead to diminished efficacy, so there is an overwhelming bias toward activation that may persist outside the developmental period. Because mood instability is an indication for use of atypical neuroleptics, concurrent use of these agents is likely, and some of them (aripiprazole) may have an additive adverse effect because of their action as a partial agonist at dopamine and serotonin receptors.

Subsequently, the risks and benefits of using SSRI medication in children, adolescents, and young adults with PWS were described [51]. The use of low-dose SSRIs in persons with PWS may have a beneficial effect on some of the characteristics of the PWS phenotype that are related to underlying anxiety and behavioral dyscontrol. In fact, very low doses of SSRIs do not affect the serotonin receptors or transporter at all. They exert fast-acting, beneficial effects by increasing production of the neurosteroid allopregnanolone (ALLO) in pyramidal cells and astrocytes [47]. ALLO stimulates inhibitory GABAA receptors by intraneuronal augmentation and extracellular neurotransmitter signaling, resulting in decreased anxiety, impulsivity, and aggression [53]. The role of neuroactive steroids in the management of stress and the treatment of affective disorders has been identified ([6, 86, 121]). The mechanism of action is not only mediated by increased inhibitory GABA tone, but also through neuroprotective effects [122].

Despite the growing awareness of mood activation associated with SSRI use as a problem, the author continues to see this phenomenon as a reason for psychiatric deterioration, behavioral crises, and hospitalization in PWS. Because the person may experience a transient improvement in mood after medication initiation due to the antianxiety effect of the neurosteroids, the SSRI may appear to be working. Then, behavioral changes may emerge gradually over many weeks and result in dose increases. Commonly, families fail to connect the behavioral changes that emerge gradually after medication dose titration, and they may suffer many months of crisis before the association is made. This relationship is further masked because the symptoms of MBA may first present with an increase in the intensity of syndromic behaviors. Psychiatrists familiar only with the symptoms of mood activation in typical persons do not necessarily recognize increased food seeking, increased skin and rectal picking, and increased perseveration as early signs of MBA in PWS. Communicating these risks to families and caregivers will enhance early recognition and management of these adverse events.

In the NIH PWS Registry data, adverse effects were not recorded. But the frequency of medication changes might indicate that when a medication was not addressing target symptoms or when side effects emerged, another medication of the same class was tried or a medication of another class, such as an SGA, was added. In some cases, a pattern became evident where a single SSRI, or

a series of SSRIs, was followed by an SGA, FGA, or AE/mood stabilizer. When this pattern occurred, it was indicative of MBA and not associated with PWS genetic subtype or age. Finally, although the dose of medication was not available in all cases in the NIH PWS Registry, the reported doses for SSRI or SNRI were within FDA guidelines or suggested parameters for treatment of depression or obsessive-compulsive disorder, for example, fluoxetine 40 mg twice daily for OCD. Although these doses may have been too high for some individuals with PWS, they were tolerated by others.

Mood and behavioral activation has been reported with other medications. It has occurred as a paradoxical effect of gabapentin and lamotrigine, methylphenidate [18], and antibiotics such as antitubercular agents (isoniazid, iproniazid), macrolides (erythromycin), and quinolones (ciprofloxacin, ofloxacin) [76].

Serotonin Syndrome

When SSRIs, SNRIs, tricyclic antidepressants, or other serotonin-acting agents (e.g., triptans, tryptophan, buspirone, mirtazapine, St. John's wort) are used alone or coupled together with lithium or some atypical neuroleptics that are serotonin agonists, there is an increased risk of serotonin syndrome (SS), a life-threatening disorder of autonomic instability, altered mental status, and neuromuscular hyper-reactivity [1]. Not all aspects of this triad may occur simultaneously. Autonomic instability includes elevated pulse rate, labile hypertension, and temperature instability. Mental status changes include confusion and agitation and can progress to lethargy and coma. Neuromuscular hyperactivity includes symptoms of hyperreflexia, spontaneous myoclonus (fast involuntary rhythmic contractions and relaxation) of the extremities and/or eyes, and muscle rigidity that can be managed with benzodiazepines. Symptoms of muscular rigidity may be less evident in PWS due to hypotonia, and temperature elevation may be unreliable due to hypothalamic dysfunction. Management depends on the severity of symptoms. Decreasing the dose or discontinuing the medicine responsible for the symptoms is recommended. Mild symptoms resolve within a few days with supportive treatment. For more severe cases, acute pharmacological treatment may include benzodiazepines and another medication such as cyproheptadine (an antihistamine that blocks serotonin receptors), chlorpromazine, or olanzapine. Scotton et al. [123] have written an excellent review of serotonin syndrome identifying the mechanism, features, differential diagnosis, and management [123].

Serotonin syndrome is differentiated from neuroleptic malignant syndrome (NMS) (see section "Neuroleptic Malignant Syndrome (NMS)") by the presence of mydriasis (dilated pupil), diarrhea, hyperreflexia, and myoclonus (including ocular clonus which is involuntary eye-rolling). Serotonin syndrome has a quick onset of occurrence (within 1 day), usually after a dose increase or the addition of a second serotonin-acting drug. Symptoms are concentration dependent and not idiosyncratic like NMS [29]. The incidence of serotonin syndrome in PWS is not known.

Adverse Effects of Antipsychotic Medications

As a class of medications, antipsychotics are divided into two groups: typical or first-generation antipsychotics (FGAs) and atypical or second-generation antipsychotics (SGAs). The FGAs, such as haloperidol, are approved for use in the typical population for symptoms of psychosis, delirium, and tics. The SGAs (risperidone, olanzapine, quetiapine, ziprasidone, iloperidone, aripiprazole, asenapine, lurasidone, and cariprazine) are indicated for treatment of psychosis, impulsive aggression, tics, and delirium. Some of the SGAs have been approved by the FDA for use as mood stabilizers. Their efficacy is based upon their capacity to block dopamine receptors while also stimulating serotonin and alpha-adrenergic receptors. They have fewer motor side effects than FGAs that predominately block dopamine receptors. Also, some antipsy-

Table 22.19 Number of antipsychotic medications used as reported in the NIH PWS Registry

Antipsychotic agent	Number used
SGA (total)	**90**
Risperidone	37
Aripiprazole	26
Quetiapine	15
Ziprasidone	8
Paliperidone	2
Olanzapine	1
FGA (total)	**10**
Haloperidol	3
Loxapine	3
Thioridazine	3
Chlorpromazine	1

Key: *SGAs* second-generation antipsychotics, *FGAs* first-generation antipsychotics

chotics function effectively as anti-nausea or antihistamine medications.

In the NIH PWS Registry data, the frequency of use of antipsychotic medications was reported (Table 22.19).

There are a few publications indicating that risperidone has been used successfully for treating the behavioral disturbances associated with PWS [4, 31, 32, 117]. Larson et al. [77] reported a case series from the UK indicating that risperidone was effective and well tolerated for the treatment of psychosis in PWS [77]. Although there is some evidence regarding the use of the SGA risperidone for the management of the extreme behavior, mood disorder, and psychosis in PWS, the actual prevalence of use of risperidone and other antipsychotics across the world is not known. Among US patients with PWS, there is a high degree of variability in the type of SGA used, and there is also a group of patients who have received typical FGAs, such as haloperidol, for many years. The incidence of adverse effects in PWS is not known, but of note, PWSA (USA) has received crisis calls about side effects over the past decade. Clearly, of all the SGAs, risperidone is the best studied among patients with developmental disabilities, as there is evidence base for its use in managing impulsive/aggressive, irritability, stereotypic, and self-injurious behaviors in children with autism spectrum disorder and other special populations.

Stroup et al. [135, 136] have an excellent review of evidence-based strategies to manage the common side effects and specific adverse events associated with the use of the SGA and FGA medications [135]. In general, four interventions are emphasized: (1) lower the dose of medication, (2) switch to another drug with a different side effect profile, (3) use a non-pharmacological intervention, and (4) use another drug to manage side effects.

Extrapyramidal Side Effects (EPS)

The major category of untoward reactions to antipsychotic medications is *extrapyramidal side effects* (EPS): tremor, cogwheeling (ratcheting movements elicited on passive range of motion of the arms and wrists), increased muscle tone (muscle rigidity) producing resistance on passive range of motion of the arms, *bradykinesia* (decreased emotional expression and slowed movement), drooling, and shuffling gait with loss of arm swing [137]. Performance of rapid alternating movements may be impaired. It is reported in the literature that the median time to onset of symptoms of EPS was 23 days with a range of 22–90 days following initiating treatment [116]. These adverse effects are managed best by reducing the dose of medication (preferred) or adding anticholinergic drugs such as diphenhydramine (Benadryl) and benztropine (Cogentin) or an antiparkinsonian medication such as trihexyphenidyl (Artane) or amantadine (Symmetrel).

When a person first begins an antipsychotic medication and the dose is being titrated, it is possible to see *akathisia* (a perception of inner restlessness in the body, especially the legs and feet with a desire to move or pace) that is managed with anticholinergic medication, benzodiazepines, alpha-agonists or beta-blockers, serotonin antagonists, or mirtazapine [135]. Within hours to days of starting the antipsychotic medication or increasing the dose, a *dystonic reaction* occurs (a sustained stiffening of muscle groups), often involving the head and neck (torticollis), that responds immediately to administration of anticholinergic medication. Other types of *dystonia* are called *oculogyric crisis*, where eye gaze is fixed upward, or *opisthotonos*, when the back

arches and the neck is extended up and backward. These manifestations also respond to prompt administration of anticholinergic medication. After a person has been receiving the antipsychotic medication for a time, late-onset (tardive) dystonic movements may occur. *Tardive dystonia* is an episodic stiffening of muscle groups to form an unusual grimace, body posture, or pose; these symptoms are more likely to occur in young males.

Among patients with PWS, muscular rigidity may not be appreciated on exam because of hypotonia, although cogwheel rigidity may be elicited. A typical presentation of EPS in a person with PWS is arms hanging down along the side of the body, which is unusual because many persons with PWS keep arms flexed, a loss of associated arm swing with walking, and a decrease in emotional expression in facial muscles. There may be drooling and shuffling gait with decreased ability to perform rapid alternating movements.

Dyskinesias

After a person has been withdrawn from an antipsychotic agent, *withdrawal dyskinesias* may occur. They are involuntary rhythmic motor movements around the face, mouth, lips, and tongue. These movements can be quite disturbing to the individual, for example, children with oral dyskinesias have been observed to put their fingers in their mouths to grab the tongue to prevent the involuntary movement. Withdrawal dyskinesias usually resolve over several weeks. When these symptoms emerge while a person is taking the antipsychotic medication, it is an indication of *tardive dyskinesia* (late-onset movement disorder), which is a permanent condition with disabling involuntary movements of the mouth, face, trunk, or extremities.

Tardive dyskinesia (TD) has been correlated with longer duration of medication use, higher dose of medication, female gender, and a history of brain injury. Discontinuation of the antipsychotic is recommended, although a challenge with an antipsychotic of a different class may help to stabilize the movements. Clozapine has been used to suppress these symptoms, and a new medication, valbenazine (a vesicular monoamine transporter 2 inhibitor), is now indicated for treatment of TD. The adverse effects of TD can be seriously disabling. Preventive strategies have included *Ginkgo biloba* extract, which appears to have some evidence base for efficacy [158]. There are some pharmacodynamic indicators of risk for EPS and/or TD involving polymorphisms of the serotonin receptors 2A and 2C. Fortunately, the incidence of these adverse effects in the general population occurs less frequently with the use of SGAs than FGAs; that is why the use of SGAs has been increasing so widely.

The incidence of withdrawal dyskinesias and tardive dyskinesias in PWS is not known, but sporadic cases have been identified [58].

Neuroleptic Malignant Syndrome (NMS)

NMS is a rare, life-threatening condition that requires emergency medical evaluation and intensive treatment, usually in the intensive care unit (ICU). It is most likely to occur early in the course of treatment with an atypical or typical antipsychotic, and there are reports that it has occurred immediately after a single injection of haloperidol [14]. It carries mortality risk of 3% with atypical neuroleptics and 16% with typical neuroleptics [143]. It is more likely to occur in males than females with a 2:1 ratio [102]. There have been at least four cases of NMS in young persons with PWS, all of which were treated successfully (Forster and Butler, personal communication). Oruch et al. [102] provide an excellent review of predisposing factors, phenomenology, differential diagnosis, and treatment of NMS for the clinician [102].

NMS presents with the acute onset of symptoms that evolve over 24–72 hours, including alteration of consciousness, muscular rigidity, fever, and dysautonomia secondary to blockade of the dopamine 2 receptor [99]. Dysautonomia includes irregular pulse, unstable blood pressure, and sweating. Drooling, incontinence, shallow breathing, tremor, shuffling gait, and agitated delirium (confusion, disorientation) can occur. Onset of fever may be delayed compared to other symptoms and may not occur at all in PWS due to hypothalamic temperature dysregulation. Further,

the hypotonia in PWS makes the muscular rigidity difficult to appreciate. Typically, laboratory testing reveals increased serum levels of creatine phosphokinase (CPK), an enzyme derived from the muscle, but in patients with PWS, CPK may not be significantly elevated due to decreased muscle mass. These factors complicate the timely diagnosis of NMS and onset of treatment in PWS. Serum levels of liver function studies and lactate dehydrogenase may be elevated. Low serum iron occurs in almost all cases, but it is not pathognomonic for NMS [78, 105]. The diagnosis of NMS is made when other causes are ruled out, such as infection, intoxication (synthetic cannabinoids, amphetamine, or cocaine), and drug toxicity (SSRI, lithium, thyroxine, or anticholinergic agents). There have been a few cases of post infectious autoimmune-related phenomena where antibodies of dopamine 2 receptor have been suspected [22]. Morbidity and mortality with NMS are associated with rhabdomyolysis (destruction of the muscle) that may lead to kidney failure.

Inpatient treatment is required. Discontinuation of the antipsychotic medication and/or administration of a dopamine agonist (bromocriptine) is recommended. The use of a muscle relaxant (dantrolene) or benzodiazepine (lorazepam) will increase GABA tone to inhibit the sympathetic nervous system. Administration of an alpha-adrenergic agonist (clonidine) will help to restabilize the autonomic nervous system. Resolution of an episode of NMS can take 2 weeks. If psychosis persists, antipsychotic medication can be resumed with a low potency agent, such as olanzapine or quetiapine, as lowest possible dose [102]. Unfortunately, concurrent use of lithium may precipitate a relapse [101].

Catatonia, Catalepsy, and Cataplexy

Catatonia is another neuromuscular syndrome that has been known to occur in PWS [26, 27, 41, 109, 146, 159]. It is a psychomotor disorder with serious consequences. It is associated with schizophrenia, bipolar disorder, and serious medical problems. Symptoms resemble NMS without the typical laboratory findings, and some researchers now believe that catatonia occurs along a continuum of symptoms with NMS [50].

Malignant catatonia and NMS are similar. Catatonia presents with muscular rigidity, waxy flexibility, and a cadre of other symptoms associated with altered consciousness (stupor) including negativity, mutism, echolalia, echopraxia, grimace, and motor mannerisms. It is caused by loss of GABA tone and is managed with lorazepam or ECT. If untreated, it progresses like NMS and can lead to organ failure and death. The use of antipsychotics is usually contraindicated because they worsen dysautonomia. Catatonia is likely to reoccur, so the use of a GABA agonist for anti-cycling (valproate, topiramate, oxcarbazepine, lithium) or an antipsychotic with low EPS (olanzapine, ziprasidone, quetiapine) is recommended in patients with psychotic conditions. The use of ECT may be aversive to some, but its success in catatonia is well documented (76% among children and adolescents), especially in cases of malignant catatonia [83].

Periodic catatonia is characterized by rapid onset, brief, recurrent episodes across the life span [60, 140]. The genetic locus for familial catatonia is located at chromosome 15q15, just outside the PWS chromosome critical region [16, 133, 134].

Catalepsy is defined as an involuntary loss of motor function and response to pain with an inability to speak despite being conscious and aware of one's surroundings. Muscle tone is most likely rigid and can be associated with bizarre body postures as seen in catatonia. Breathing and pulse rate can be difficult to detect, and historically people with catalepsy have been thought to be dead. The key difference between catatonia and catalepsy is that in catatonia the person is delirious and not responsive to what is going on in the environment, while in catalepsy, the person is aware but unable to actively respond. Catalepsy has been seen in PWS and has been associated with stress or psychosis. Also, it can be seen as a result of medications that cause dopamine 2 receptor or alpha-1 adrenergic receptor blockade, acetylcholine agonism, or antagonism of glutamatergic neurotransmission, especially that of N-methyl-

D-aspartate (NMDA) receptor [156]. It has also been seen after abrupt withdrawal of SSRI antidepressants or stimulants after chronic administration. It is managed with a supportive environment and antianxiety agents such as lorazepam. Like catatonia, there is evidence of a hereditary mechanism that has been well defined in rodent models, associated with polymorphisms of the serotonin 1A receptor (decreased function) and tryptophan hydroxylase (increased function) [74].

Cataplexy is defined as a sudden and transient loss of muscle tone associated with full conscious awareness. It is not related to the use of neuroleptics, but it can be seen when SSRI treatment is interrupted or withdrawn suddenly. It is often associated with strong emotions such as laughing, crying, anger, or terror. Cataplexy is most often associated with narcolepsy, a sleep disorder that can be seen in PWS [152].

Weight Gain

Almost all atypical antipsychotics result in a tendency toward weight gain in typical persons, and although it is associated with duration of exposure [2, 141], studies suggest that it can be observed with in the first six weeks of treatment. This side effect is related to the effect on dopamine 2, serotonin 2C, and histamine receptors. In a recent meta-analysis of 307 papers, the only atypical antipsychotics that were weight neutral were amisulpride, aripiprazole, asenapine, lurasidone, and ziprasidone (www.ncbi.nim.nih.gov, 2014). However, clinical experience with aripiprazole in children and adolescents with ASD (autism spectrum disorder) suggests that weight gain has occurred. Paliperidone, risperidone, and quetiapine have moderate weight gain. Olanzapine, chlorpromazine, and clozapine are associated with the largest increase in abdominal circumference, weight gain, and metabolic changes. Guidelines for using atypical antipsychotics suggest monitoring BMI and waist circumference, blood pressure and pulse, fasting lipids, cholesterol, and blood sugar [7]. Medications for the management of metabolic symptoms associated with atypical antipsychotics include metformin and melatonin [63, 79].

Atypical antipsychotics are associated with weight gain because they produce an increase in appetite. Because the mechanism for hyperphagia in PWS is a satiety deficit, it is not inevitable that a person with PWS receiving these medications will gain weight. Further, those individuals who have environmental management of their food and a healthy exercise program are unlikely to gain weight. In the clinical experience of this clinician (JF), weight gain has been an uncommon occurrence. A retrospective case-controlled study of 52 pediatric and 92 adult PWS patients at the Children's Institute (TCI) looked at BMI and the metabolic side effects of antipsychotic medications prescribed on admission and during the course of hospitalization and concluded that weight loss was less among those receiving antipsychotics, but minimal metabolic changes were noted [36].

Hyperprolactinemia

Hyperprolactinemia is a side effect of some antipsychotics, such as risperidone, haloperidol, chlorpromazine, and perphenazine; it occurs 20% of the time. The major consequence of hyperprolactinemia is gynecomastia, and this is especially a problem among young males. In addition, galactorrhea can occur in women. Hyperprolactinemia is a result of dopamine 2 receptor blockade (DR2) in the pituitary. Not all atypical antipsychotics have the same propensity for causing hyperprolactinemia; aripiprazole does not (www.ncbi.nlm.nih.gov). In fact, adding aripiprazole at low doses (2 mg/day) is effective in reducing prolactin levels due to its partial D2 agonism [157].

Hypothermia

Another side effect of atypical antipsychotic medication is hypothermia. There have been less than a dozen reports of hypothermia in PWS [108]. Additional medications, such as beta-adrenergic blockers, may also cause hypothermia. It can be recurrent in those who are susceptible, and it can be lethal. If it is not recognized, it carries a high multisystem morbidity [45, 139]. Temperature instability is related to hypothalamic dysfunction in PWS, and both

hyperthermia and hypothermia can occur. A review of this phenomenon can be found at www.pwsausa.org/medical-issues-a-z/. Another naturalistic study at TCI found that atypical antipsychotics did not contribute to body temperature changes [17].

Dysautonomia and Cardiac Risk

PWS is believed to have an imbalance in the autonomic nervous system (ANS) that contributes to hyperphagia [55], stress sensitivity, and behavioral problems (tantrums) [87]. Studies suggest that heart rate variability (HRV) in PWS is reduced due to decreased vagal tone [28, 114]. There is a high degree of psychiatric comorbidity in PWS with mood and anxiety disorders, psychosis, and autistic spectrum disorder. All psychiatric disorders (especially psychoses) are known to reduce parasympathetic activity, which decreases heart rate variability and adds to the burden of cardiovascular risk and dysrhythmias [3]. Also, this occurs with psychotropic medications, especially atypical antipsychotics and agents with anticholinergic, alpha-adrenergic agonistic effects, and beta-adrenergic blockade [64]. According to Iwamoto [66], there is a threshold effect for the dose of antipsychotics and anticholinergic agents on the decline in ANS function [66]. This threshold for antipsychotics is 1078 +/− 883 mg/day (chlorpromazine equivalent), and the threshold for anticholinergic agents is 3.2 +/− 1.5 mg/day (biperiden equivalent). The publication by Inada and Inagaki [65] has an extensive data base on dose equivalencies for antipsychotic, anticholinergic, antidepressant, and anxiolytic agents (http://www.jsprs.org/en/equivalence.tables/). The equivalent doses of some commonly prescribed medications for patients with PWS are located in Table 22.20.

Further, a dose-related prolongation of the QTc interval is reported in some first- and second- generation antipsychotics (see Fig. 22.4). In a study of 116 children and adolescents <18 years of age monitored for 1 year after the initiation of antipsychotic medication, 2 patients receiving risperidone experienced QTc lengthening which resulted in the discontinuation of the medication [20]. Aripiprazole was associated with an increase in pulse rate over time, but QTc was unchanged. Although the majority of patients did not experience a change, the monitoring of cardiovascular parameters is recommended. Practice guidelines are available online at https://www.nice.org.uk/guidance/qs102/chapter/Quality-statement-6-Monitoring-for-side-effects-of-antipsychotic-medication [98]. Chong et al. [19] have written an excellent overview of the cardiac and other risks associated with antipsychotic medications [19].

Adverse Effects Associated with the Use of Anti-epileptics and Mood Stabilizers

According to the NIH PWS Natural History Registry, there was a bimodal distribution of the use of anti-epileptic/anticonvulsant medication. In the younger group, the medication was used for seizure management. In the older group, these medications were used mostly for the management of mood and behavior.

Table 22.20 Equivalent doses of medications contributing to ANS dysfunction

Antipsychotics mg/day		Anticholinergics mg/day		Antidepressants mg/day		Anxiolytics mg/day	
Aripiprazole	4	Amantadine	100	Clomipramine	120	Alprazolam	0.8
Chlorpromazine	100	Benztropine	1	Duloxetine	30	Clonazepam	0.25
Haloperidol	2	Biperiden	2	Escitalopram	20	Diazepam	5
Olanzapine	2.5	Diphenhydramine	30	Fluvoxamine	150	Lorazepam	1.2
Paliperidone	1.5	Hydroxyzine	65	Imipramine	150		
Quetiapine	66			Mirtazapine	30		
Risperidone	1			Paroxetine	40		
				Sertraline	100		
				Trazadone	300		

Carbamazepine/Oxcarbazepine

A severe *body rash* (Stevens-Johnson syndrome or toxic epidermal necrolysis) can be seen, and screening for human leucocyte antigens A and B (HLA-A, HLA-B) is recommended by the FDA before starting this medication. Certain polymorphisms of HLA-A and the presence of HLA-B are associated with ethnic groups and increased risk of rash. The appearance of a rash constitutes a serious health concern, and the person will require evaluation in an emergency medicine department. *Hyponatremia* is a common finding when these agents are used in typical persons, especially at a younger age [37]. However, in persons with PWS, a clinical case series suggests that almost everyone with a dose of over 600 mg per day is at high risk for hyponatremia (Dr. Linda Gourash, personal report). Hyponatremia can be low enough (<130 mm/L) to precipitate seizures and almost always requires medical management. Hyponatremia can also be caused by SSRIs, FGAs, and SGAs (except risperidone), so using these medications in combination with carbamazepine or oxcarbazepine results in an additive risk [38]. In most cases, hyponatremia is due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Lithium can be used together with carbamazepine or oxcarbazepine to manage hyponatremia by decreasing the kidney's ability to concentrate urine by blocking the effect of antidiuretic hormone (ADH); this eliminates free water, normalizing serum sodium levels [39].

Valproic Acid

Depakote (brand name) is indicated for treatment of impulsive aggression, bipolar disorder, migraine, and seizure disorder. It can be a highly effective agent for managing the severe disruptive behaviors and mood instability associated with PWS phenotype. However, clinical experience using this medication in adolescents and adults with PWS led to the finding that nonhepatic hyperammonemia appeared 90% of the time at some point during the transition from adolescence to adulthood [150]. This finding can be seen in typical persons with seizure disorders at a frequency of 20–50%, especially among those who require more than one anticonvulsant to stabilize. In a case series of psychiatric patients ($n = 123$) receiving valproate for mood stabilization, 51% of patients had hyperammonemia, but it was difficult to differentiate symptoms of hyperammonemia from underlying mental status aberrations [115]. Because the symptoms of hyperammonemia may overlap with the PWS phenotype (lethargy, hypotonia, agitation, ataxia, cognitive slowing, or confusion), it may be difficult to ascertain the extent of adverse effects on a clinical basis alone, so monitoring plasma ammonia is recommended, especially in patients of transition age. Also, the use of another anticonvulsant or an antipsychotic medication, especially risperidone, contributes to hyperammonemia [23]. The management of hyperammonemia usually involves reducing the dose or discontinuing the valproic acid. Because valproate interferes with the reuptake of glutamine, which causes increased ammonia production, and promotes carnitine elimination through the kidney, administration of L-carnitine together with valproate decreases serum ammonia levels [10, 15, 93, 147]. Lactulose has also been used, but its efficacy is related to producing diarrhea.

Topiramate

Topiramate at low doses has been shown to be effective in managing the skin picking behavior associated with PWS [129, 132]. Weight loss and improved scores on the Dykens Hyperphagia Scale were demonstratewd in an eight-week, double-blind, randomized controlled study in PWS at doses of 50–200 mg/day [21]. However, because topiramate is a carbonic anhydrase inhibitor, it can affect serum electrolytes and cause a hyperchloremic acidosis due to failure of the kidneys to resorb bicarbonate [119, 130]. Topiramate decreases urine acidity, leaches calcium from bones, and increases the risk of kidney stones fivefold [85]. Altered mental status (somnolence, irritability, and sensory abnormalities) has been reported in typical persons, and irritability was noted in a case series in PWS together with renal tubular acidosis [52]. Adverse effects are dose related, and in the extreme, cardiac arrhythmias have been reported. Also,

hypothermia and hyperammonemia have been reported, especially when taking valproate concurrently [72].

Lithium Carbonate

Lithium carbonate is the gold standard for treatment of bipolar disorder, but it is also indicated for impulsive aggression, self-injurious behavior, treatment-resistant depression, and cyclic psychosis. Clinical experience suggests that it is effective in PWS as well as other special populations for these symptoms [92]. There are some side effects which must be monitored. There is a risk of lithium-induced hypothyroidism, which occurs in about one-thirds of patients, and hyperthyroidism, which is relatively rare. After chronic administration, lithium-induced hyperparathyroidism may occur, and this is detected by elevated serum calcium levels together with elevated parathormone levels. This condition responds to a decrease in lithium dose; rarely, discontinuation of lithium is required. Over time, renal function can become impaired; renal toxicity can be minimized by once-daily administration. Hypernatremia may occur due to nephrogenic diabetes insipidus, which interferes with the kidney's ability to concentrate urine [39]. There is risk for bradycardia related to the effect of lithium on the sinoatrial node in the atrium of the heart. Symptoms of dizziness, fatigue, palpitations, and nausea may occur idiosyncratically at any drug level. In this rare condition, ECG will demonstrate sinus bradycardia, flattening of the T wave, and bundle branch block below the S-A node. Symptoms remit when lithium is discontinued. Lithium may cause an increase in the white blood cell count. It may cause acne if patients with PWS are receiving gonadal steroid therapy.

Gabapentin

Although gabapentin (Neurontin) is in the medication class of anticonvulsants, it has weak antiepileptic and mood stabilization effectiveness. It has been used widely for the management of neuropathic pain, which is rarely an issue in PWS. However, gabapentin holds promise as an antianxiety agent [49]. It is effective in increasing GABA without direct effect at the receptor, which is highly desirable because GABA receptors are decreased in PWS [84]. Gabapentin is only effective for 6–8 hours, so it must be administered several times per day. It is excreted by the kidneys unchanged, and as a result, it must be used with caution in individuals with renal insufficiency. It has been known to cause hyponatremia in middle-aged females, especially with those who have had brain injury. Although other gabapentinoids are controlled substances, gabapentin is not addictive, although it can produce withdrawal symptoms when precipitously discontinued [142].

Summary, Conclusions, and Recommendations

Prader-Willi syndrome is a neurodevelopmental genetic disorder with a complex behavioral phenotype that has high comorbidity with a variety of psychiatric disorders resulting in the use of multiple classes of psychotropic medications, often at the same time. Polypharmacy increases the risk of drug interactions and side effects. The approach to pharmacological treatment of symptoms and comorbid disorders associated with PWS should consider the following guidelines that have been discussed throughout this chapter:

- Begin or taper one medication at a time.
- Use the lowest dose of medication possible and titrate slowly, measuring both target symptoms and side effects.
- Use short-acting medications to establish lowest effective dose before switching over to long-acting preparations.
- Because of the decreased lean muscle mass in PWS, the use of intramuscular (IM) or depot antipsychotic medication is discouraged.
- Risperidone is the best studied SGA and has a track record for use to manage behavioral difficulties associated with ASD, other IDDs, and PWS; adverse drug effects and potential drug-drug interactions are well known.

- There is minimal evidence for efficacy of using more than one SGA at a time.
- When using SGAs or FGAs for psychotic conditions, do not use anticholinergic drugs prophylactically; if extrapyramidal effects occur, reduce the dose of SGA or FGA or switch to another agent.
- Although SGAs have the potential for increasing eating behavior among typical persons, there is less evidence that this occurs in PWS, especially under conditions of food control and psychological food security (FOOD SECURITY).
- A review of diagnoses, genetics, and treatment approaches in PWS can be found in Butler, Miller, and Forster [13].

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The Psychiatric Phenotype in Prader-Willi Syndrome

23

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Introduction

Prader-Willi syndrome (PWS) is caused by the loss of expression of contiguous paternal genes both inside and outside the imprinted region on ch15q11-13. Gene expression is related to the genetic subtype caused by either deletion, maternal uniparental disomy 15, or an imprinting center defect. The PWS genotype (DEL, UPD, IC, or others) provides the genetic blueprint that interacts with the normal processes of neural development, experience, and learning to produce lasting effects on the structure and function of the brain. The loss of expression of paternal genes has an enduring impact that interferes with the ability to adapt to the environment from both inside and outside the body. A feedback deficit model describes the intrinsic dysfunction in neural and endocrine pathways that creates functional physiologic dysregulation. And in the brain, there is an imbalance in excitatory (go, do) and inhibitory (stop, don't do) mechanisms. These nervous system regulation deficits illustrate the complex, ongoing interaction between brain/body dysfunction and behavior in PWS. The intrinsic deficits in the brain/body interaction are constantly seeking to correct the imbalance, but the result cannot be sustained. The behavioral phenotype is the manifestation of this intrinsic, automatic coping strategy driven primarily by the hypothalamus and insula in the brain [48, 55, 81]. The neuropsychiatric phenotype of PWS evolves over the course of development; it is the tip of the iceberg of neurodevelopmental differences in PWS. This chapter covers a literature review of studies describing the behavioral phenotype; a psychiatric evaluation, neurodevelopmental case formulation, and differential diagnosis; and a descriptive narrative of psychiatric diagnoses as they appear across developmental stages from early childhood through senescence.

The Behavioral Phenotype

Among individuals with developmental disabilities, especially those with genetic etiologies, some temperamental and behavioral characteristics are so commonly present that they are considered to be part of the *behavioral phenotype*. A behavioral phenotype is defined as a spectrum of traits that "cannot be accounted for by other variables such as IQ or adaptive behavior" [94]. Clinicians and researchers have used different approaches to define the behavioral phenotype of PWS: a developmental model, a behavioral

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assessment model, and a descriptive/phenomenological model.

In the developmental model, the behavioral phenotype in PWS is derived from early childhood behaviors that appear in a predictable sequence similar to that seen in typical development. This sequence in typical children is "hard wired" and determined by underlying brain development. Behaviors appear as part of a developmental stage and diminish as a new stage begins. Developmental theorists speculate that these early childhood behaviors emerge to manage the anxiety caused by the unpredictability of the environment. The need for these behaviors gradually diminishes over time as the typical child acquires a greater capacity for self-regulation (response inhibition) and management of anxiety (emotional control) [85]. In PWS, the staging process unfolds, but the time course is delayed, the behaviors are more intense, and the duration of each stage persists much longer than expected. As these immature stages persist, they interfere with the acquisition of new behaviors based on learning and experience. The capacity for self-regulation and emotional control is diminished in PWS, so developmental persistence of these immature behaviors continues into adulthood.

Further, stress sensitivity and anxiety persist throughout development. According to the data from the FPWR Global Registry, anxiety occurred in about 50% of youth; it increased throughout the early years and peaked from 10 to 14 years of age [10]. Anxiety was twice as frequent among UPD than DEL [58]. Repetitive questioning emerges as soon as a child begins to speak and peaks around age 10 years at the same time as anxiety and tantrum intensity. Cognitive rigidity and perseverative behaviors create "slow torture" for parents (JF, "personal communication"), and many parents accommodate to avoid conflict. Families with the highest degree of structure, consistency, and predictability in their homes report less stress [29, 30]. The burden on the parent increases after age 12 due to the frequent disruption of daily routines and constraints on social activities [54]. The most important behavioral priorities for families are hyperphagia, anxiety (repetitive speech and behavior), tantrums in response to change, and intellectual functions (thinking, problem-solving, learning, and speech) [84]. These problems are the reasons that families seek mental health evaluation and counseling.

In the behavioral assessment model, various instruments have been used to define the characteristics of the behavioral phenotype of PWS, including the Child Behavior Checklist (CBCL), Aberrant Behavior Checklist (ABC), Developmental Behavior Checklist (DBC), and others. Early studies used a broad age range of subjects and did not select for genetic subtype. This has made comparisons difficult across studies. Also, whereas some phenotypic behaviors are stable over time, others wax and wane and have a more episodic course. There is general agreement that behaviors are often situationally reactive and dependent on environmental contingencies [23].

The descriptive phenomenological model is based on considerable clinical experience with PWS. In this model, there is also an appreciation that some of the core phenotypic characteristics occur in a dynamic flux with environmental factors and level of stress. Thus, measurement of the phenotype may be situation dependent. Just as repetitive and stereotypic behaviors may help to manage the anxiety of uncertainty in early childhood, phenotypic behaviors may represent a coping strategy. Table 23.1 itemizes the behavioral assessments and phenomenological descriptions of the PWS phenotype.

Psychiatric Evaluation, Mental Status Examination, and Case Formulation in PWS

Prader-Willi syndrome is unique among all other developmental disabilities because of the high degree of environmental supports that are needed to keep individuals safe. Families report that in addition to controlling the food, there are challenges related to the behavioral phenotype, such as repetitive asking and doing, egocentrism and rigidity, tantrums, hoarding, and skin picking.

Table 23.1 Behavioral assessment and descriptive phenomenology of the PWS phenotype

Bartolucci and Younger [5]	Descriptive	Temperamental (oppositional, explosive, and antisocial) driven by underlying biologically determined anxiety; psychotic thinking with delusions, either latent or displayed; and a "refusal lethargy" set (shutdowns) in response to environmental situations similar to lethargic depression
Dykens and Cassidy [23]	Descriptive	Irritability, argumentativeness, lability, stealing (primarily food or money for food), skin picking, and repetitive actions
Clarke et al. [13]	ABC (Aberrant Behavior Checklist)	Temper tantrums, self-injury, impulsiveness, lability of mood, irritability, inactivity, and inappropriate and repetitive speech
Moldavsky et al. [57]	Descriptive	Hyperphagia due to lack of satiety; obsession for food, nonfood items, temper tantrums, impulsivity, and aggression
Pittsburgh Partnership [36]	Descriptive	Food-related, anxiety and insecurity, cognitive rigidity, oppositional defiant behaviors, and skin picking
Whittington and Holland [94]	Descriptive	Excessive eating, repetitive and ritualistic behavior, skin picking, temper outbursts, lying and stealing, reduced activity level, and mood and sleep disturbances
Skokaukas et al. [77]	CBCL/6–18 (Child Behavior Checklist)	Thought problems, attention problems, social problems, withdrawn/depressed, and somatic complaints
Jauregi et al. [43]	DBC-A (Developmental Behavior Checklist-Adult)	Disruptive, self-absorbed, communication disturbance, anxiety/antisocial, social relating difficulty, and depression
Avrahamy et al. [3]	Descriptive	PWSBQ (validated on HQ, CBCL, and CGI): Food-related behavior, oppositional defiance, anxiety/insecurity, cognitive rigidity/inflexibility, and skin picking
Thuilleaux et al. [83]	Descriptive	Basic (hyperphagia, arousal deficits, social skills, impairments, lie/steal/collect/hoard, rituals, contextual disruptive behavior, skin picking/SIB), impulsive, compulsive, and psychotic
Pittsburgh Partnership [37]	Descriptive	PWSPQ: Food-related drive behaviors, nonfood "excessive/repetitive" drive behaviors, skin picking, cognitive rigidity, disruptive behavior, and stress sensitivity/mood symptoms
Gantz et al. [33]	GAIB (Global Assessment of Individual's Behavior)	Food-related behavioral problems, nonfood-related problems, food-related obsessive speech and compulsive behavior, nonfood-related obsessive speech and compulsive behavior, and level of interference with daily function
Shelkowitz et al. [71]	Descriptive, data from the Global PWS Registry	Neuropsychiatric features (sleep, seizures, psychiatric symptoms) in 893 respondents; anxiety and compulsive behaviors were the most prominent

Sometimes a mood change, unusual thinking, disorganized behavior, or confusion may occur. Psychiatric symptoms interfere with persons' ability to function over a specified time period, which brings them into conflict with expectations. Symptoms reflect a change in the pattern of thought, behavior, or emotion. Often, the persons will try to cope the best they can, which may result in an intensification of symptoms (maladaptive behavior), or the parents/carers will accommodate, which may inadvertently reinforce the problem(s). Referral for evaluation often occurs after a pattern of maladaptive behavior has been established. Smoldering symptoms may erupt in a crisis producing high-intensity behavior such as impulsive aggression, property destruction, shutdowns, theft, self-injury, or running away. A crisis may threaten the integrity of the person's living situation whether it is at home with parents or in a group home. In some cases, law enforcement has become involved, the person has been arrested, and a court hearing is pending. In the school situation, the crisis may pertain to the disruption of the daily routine that

deleteriously affects the learning of the other students. Or the person may have made an allegation of abuse or told a lie which precipitates an investigation by child or adult protective services, and the opinion of the neuropsychiatrist may be essential to determine what will happen next.

Because of the high degree of infrastructure required to manage the phenotypic behaviors in PWS, the environment becomes the "shadow patient" in the evaluation process. From the outset of this multifaceted evaluation, it is essential to determine the reason(s) for the evaluation from the many perspectives of the "stakeholders." It is highly unlikely that the person with PWS will have requested the evaluation. It is most likely that the evaluation has been scheduled by the parent or carer. The patient may already have a behavioral treatment team in place, so knowledge of current and prior interventions is helpful to understand the presenting behavior within a transactional model. In this regard, the environment becomes a focal point of the evaluation. Also, each stakeholder in the evaluation (patient, parent, carer, school, service provider, or legal representative) may have a different expectation for the outcome of the evaluation. Although arriving at a diagnosis is the preferred outcome for the psychiatrist, everyone else may want to know what caused the problem and what can be done to "fix it." There will be tremendous pressure to prescribe a medication to take the symptom(s) away, but medication may not be the most important part of the treatment plan.

The age of the patient is an important consideration. If the patient is an adolescent or younger, the parents are likely to be consenting for the evaluation and treatment. If the patient is a young adult or older, and guardianship has not been determined, the patient will be consenting for themselves. Most of the time, this situation can be handled with supported decision-making [17, 70]. But in some circumstances, the patient will demand to be in charge and refuse to consent for evaluation and treatment. This will present as a challenge because IQ does not determine mental capacity, legal capacity, or competency in PWS. Even the highest functioning person with PWS will have difficulty making sound decisions when food, money, exercise, level of independence, and relationships are considered. Their capacity to understand informed consent is limited, and even if they can repeat the information back to the clinician accurately, their ability to use this information at a future date may be impaired. Therefore, the PWSA USA recommends legal guardianship for adults with PWS. Sometimes, a durable power of attorney (POA) for medical concerns may suffice in emergency situations such as hospitalization. But the scope of the POA is not adequate for the other aspects of the person's life as mentioned above. This continues to be a controversial topic especially in international circles where the potential for discrimination against people with mental disabilities is taken very seriously. There is strenuous rejection of the idea that a person's mental capacity can be determined by a diagnosis [16].

For the initial evaluation, additional time will be required both for the patient with PWS, their parents or carers, and team members. While the person with PWS may be able to share their thoughts and feelings in the moment, they may not be reliable historians, especially with respect to recall of emotional states within time frames. Also, their understanding of a situation may solely focus on their point of view (like a young child), and they may be unable to accept a reality-based challenge. Their episodic memory is better than declarative recall, but if you ask them to tell you the story of their symptoms, they may weave extraneous details from other sources (TV programs, news reports, conversations between parents and carers, or overheard telephone conversations) into their personal narratives. Therefore, parents and caregivers must serve as co-informants to validate all aspects of the history (identification of problems, symptom severity and time course, level of impairment, and family and medical histories) *in the absence of the patient*. During this collateral interview, patients must be supervised, so it is helpful to advise the parent or caregiver to bring a sitter. As with other developmental disabilities, it is best for the clinician to take the lead from the parents about how to communicate most effectively with

the patient for the clinical interview and mental status examination. It is equally as important to establish rapport with the parent, carer, and team as well as with the patient.

In PWS, more than any other developmental disability, it is essential for the psychiatrist to evaluate whether the environmental structure of living is meeting the person's needs. This is why the environment becomes the "shadow patient" in the evaluation process. The best practice guidelines for the environmental management of syndromal behaviors include a scheduled meal plan with food security, restricted food access, a plan for daily activities, mandatory exercise, opportunities for sensory experiences, low expressed emotion by caregivers, and clear behavioral expectations with reinforcement [67]. A good daily plan will alternate the schedule of preferred and nonpreferred activities and may be augmented with incentives. Bribery and punishment are not effective, and food reinforcers are not recommended. Natural consequences are the best feedback. It should be noted that *not everyone with PWS has the same drive for food*, although food security is essential for all.

When a psychiatrist evaluates a patient with PWS, it is important to establish a behavioral and psychological baseline and how the current symptoms interfere with the patient's level of adaptive functioning. It is important to know the genetic subtype, the level of intellectual function, the learning challenges determined by WISC-R or WAIS or equivalent, the recent changes in the caregiving or environmental context in which the person lives, and the new onset of medical problems. An instrument such as the PWSBQ or the PWSPQ is helpful to determine a baseline of phenotypic behaviors. Then, the source and magnitude of stress must be ascertained, realizing that the stress may be environmental or internal. *Always consider the significance of the stressor from the person's perspective.* Often, behavioral problems emerge when the person is trying to cope with stress and runs into conflict with environmental expectations. Then, the behavior is considered maladaptive. Stress may be due to loss, change, disappointment (may be related to false expectations), environmental insufficiency, or too high expectations from caregivers. Loss or change of the person who oversees *food security* and daily schedule may precipitate uncertainty resulting in increased anxiety and behavioral change. Medical stressors may be somatic (systemic infection, cellulitis, constipation, orthopedic problem), dynamic (endocrine, cardiopulmonary, sleep apnea), or iatrogenic (medication reaction or interaction).

One of the goals of the initial evaluation is to determine the nature and scope of the person's needs and the degree to which the caregiving environment can meet those needs. Always consider that a source of stress contributing to the presenting problem may be environmental insufficiency. This has been especially important during the COVID epidemic when both the level and consistency of supervision have been compromised, as workshops, day programs, and schools either have closed or substituted virtual instruction, resulting in decreased opportunities for environmental enrichment [4].

The Developmental Mental Status Examination for PWS

Appearance Appropriateness of dress for season and outside temperature, congruence of appearance with age and gender, complexion and eye color (DEL are more fair with blue eyes), weight and stature (truncal obesity is common), competence of gait and posture (may be affected by scoliosis), position of arms and hands (usually flexed at the waist, sensitive to extrapyramidal side effects resulting in arms hanging down with loss of associated arm swing with walking), facial dysmorphisms (almond-shaped eyes, corners of the mouth downturned), extremities (small hands and feet), and anatomical distribution of picks, if present (note if fingernails are too long and ungroomed), note if wearing glasses. Growth hormone normalizes stature, body composition, and facial dysmorphisms. If the person is obese, check for non-pitting leg edema.

Demeanor Eye contact (often decreased due to inability to attend to more than one sensory modality simultaneously, for example, cannot look and listen or speak at the same time), degree of politeness, appropriateness, and compliance with requests.

Psychomotor Activity Stereotypic or repetitive behaviors (if actively skin picking, note degree of redirectability to *fold your hands* with a verbal and gestural cue); motor tics or tremors; muscle tone, joint flexibility, and rapid alternating movements; and degree of somnolence during the interview

Speech and Language Describe speech tone (usually hypernasal) and prosody (usually minimal tonal variation); production (may be limited to a few words or may be able to tell a story); fluency (some stutter with associated eye flutter); articulation and intelligibility (usually impaired, especially among DEL); presence of sticky saliva, drooling, and dental problems; degree of speech processing delay [80] (interviewer may need to repeat the question or have the person state what was just asked); developmental level of vocabulary, grammar, and complexity of syntax; capacity to sustain eye contact and conversation; and ability to carry a tune, *singing the Happy Birthday song* (most do not have a good sense of pitch).

Affect Describe observed facial expression (range, valence), usually blunted or constricted (emotional expression may be decreased due to extrapyramidal effects of neuroleptic medication), and may display grimace.

Mood Person's description of their emotional state (happy, sad, angry, etc.) – use a visual analog for intensity, "big sad, medium sad, and little sad," or frequency, "most days, some days, and few days"; it may be difficult to elicit a time frame for mood change. A change in interest in pleasurable activities is the best indicator for high or low mood. Energy level, sleep, and appetite are less reliable indicators. Because the concept of anxiety may be difficult to comprehend, a direct inquiry about worries, apprehension (feeling that something bad is going to happen), or fears may be necessary.

Thought Process Rarely linear and goal directed; usually circumstantial, digressive, and perseverative; and confabulation (storytelling that the person believes to be true). For a full description of the phenomenon of confabulation in PWS, see famcare@ipwso.org/confabulation.

Thought Content Recurrent thoughts or worries about food, events, activities, relationships (friends, romantic attachments, family, or carers), or behavior; explore mood-congruent thoughts (guilt, low self-esteem, self-depreciation; elevated self-esteem, overestimation of abilities); incidents of being wronged with or without ideas of revenge (assess dangerousness); obsessions (intrusive thoughts that cause discomfort are uncommon); awareness of compulsions (limited insight into problems caused by excessive repetitive behaviors or collections); magical thinking (typical of younger children but may persist into adulthood in PWS; and may be elaborated in content like an imaginary companion, or believing that people on TV are real); fantasies (alternative reality that is acknowledged as not real, but in PWS may seem real to the person at times, such as an identification with a superhero or wishing something was true like a psychological defense against disappointment); and delusions (fixed false beliefs) of paranoia, persecution, jealousy, or grandiosity. When inquiring about an act of nonfood theft, it is important to understand the person's point of view, for example, many will say that the object was theirs and they found it. If the person is depressed, it is important to inquire about suicidal ideation and plans, especially among high functioning persons with PWS. In some cases, it will be clear that threats of suicide are manipulative (going to the emergency room will result in food acquisition). In other circumstances, the person may want to die to escape the restrictions related to PWS; disposal of treasured possessions may be an ominous sign.

Cognitive Testing Comment on attention, distractibility, concentration, and processing speed while ascertaining birthdate, age, address, and telephone number; orientation (date, time, and location); three-word registration and recall; digit span forward and backward (some may not understand the concept of backward even with a demonstration); draw a person (male, female, self); draw a clock (not digital); handedness; left/right distinction on self or others; ability to follow simple directions, motor imitation, and ideomotor imitation ("show me how you brush your teeth"); modified trails A (to assess cognitive flexibility); a go/no-go task (to assess inhibition); verbal fluency by semantic category ("how many animals in the zoo can you name") and phonetic category ("name all the words you can think of that start with the letter F"); and abstraction of similes. People with PWS will always perform best on tests that include references to food. The Montreal Cognitive Assessment (MoCA) is a comprehensive neuropsychological screening tool that has been used successfully in PWS. It assesses many of the above cognitive abilities (https://www.parkinsons.va.gov/resources/MOCA).

Insight and Judgment Ask "What is Prader-Willi syndrome? One high functioning person described PWS as "food deficit disorder" (Linda Gourash, "personal communication"). *Persons with PWS display impaired judgment regardless of age, IQ, or verbal language abilities.* Often, they have limited insight into their symptoms or the impact of their behavior on others, despite the ability to find fault with others who do not follow the rules (PWS police) [67].

The Neurodevelopmental Case Formulation

The neurodevelopmental case formulation is an essential step for complex decision-making leading to differential diagnosis and treatment planning; it also provides an outline for developmental interviewing [44]. It organizes all pertinent clinical information into predisposing, precipitating, perpetuating, and preventative factors:

- *Predisposing factors* include genetic subtype, age, comorbid medical diagnoses (sleep apnea, scoliosis, endocrine deficiency), IQ/LD (cognitive impairments result in problem-solving deficits), speech/language disorder, impaired social skills, poor coping strategies, family history for psychiatric disorders, and untoward reactions to psychotropic medications.
- *Precipitating factors* are usually stress-related emanating from a change in the environment, such as food access/availability; change in structure, consistency, level of support, and/or supervision from parents, educators, or carers; unrealistic expectations for adaptive skills or academic performance; unhelpful carer attitudes (punitive interactions); or interpersonal conflict (bullying situations, exploitation, or abuse). Environmental stress can be as simple as the onset of a new school year or as complicated as iatrogenic causes (most likely to be a medication side effect or drug interaction).
- *Perpetuating factors* are related to ongoing stress due to food insecurity or environmental insufficiency; behavioral accommodation by parents, educators, or carers; inadvertent reinforcement of maladaptive behavior (secondary gain from repeated hospitalizations, trips to the emergency department, or involvement of law enforcement, all of which result in unplanned food access); chronic interpersonal problems; punitive attitudes or use of punishment or bribes; and untreated medical or psychiatric conditions. Intrinsic factors include chronic communication problems due to speech and language disorders, undiagnosed learning disabilities (especially nonverbal learning disorders), unrecognized drug reactions (especially mood and behavioral activation), or implementation of the wrong treatment plan (using medication when psychological or behavior therapy is indicated).
- *Preventive factors* that minimize the risk for psychiatric and behavioral symptoms include deletion subtype; a higher IQ (may improve

problem-solving but not judgment); an easy-going temperament; flexible and resourceful caretakers; goodness of fit between the person, the environment, and the carers; daily PWS programming with consistency of expectations, predictability of the daily routine, scheduled opportunities for work, learning, and preferred activities; food control, *food security*, and mandatory exercise; opportunities for socialization with peers; ongoing involvement with an informed family; opportunities to practice religious beliefs; and a good working relationship between the person, parent/guardian, school, and residential provider.

Psychiatric Diagnosis in PWS

Almost every person with PWS undergoing a psychiatric evaluation will meet criteria for the PWS Personality (personality change due to a medical condition, DSM-5: F07.0) [2, 27]. The DSM-5 criteria for this diagnosis is an impairment or disturbance in adaptive function directly attributable to an underlying medical condition (PWS). The cluster of additional specifiers for this category includes affective lability, disinhibition, aggression, apathy, and/or paranoia. The behavioral phenotype of PWS defines the PWS Personality. Changes in the severity of these phenotypic behaviors are clues to look for alterations in mental state that might indicate the presence of a psychiatric disturbance. Further, all the characteristics of the behavioral phenotype may become exaggerated with stress. These features are the "background noise" when considering the differential diagnoses in patients with PWS.

Psychiatric evaluation will define symptoms, determine their duration, and ascertain the patient's level of impairment. The developmental case formulation will place these symptoms within the multifactorial context of predisposing (attributes), precipitating (environment), perpetuating (experience), and protective (resilience) factors. The differential diagnosis will take these factors into consideration and determine whether the patient has a PWS Personality *plus* a comorbid psychiatric illness related to stress from the environment, a medical condition, an iatrogenic effect of medication, a learning problem, an intellectual deficiency, or another major psychiatric condition (mood, cognitive, or psychotic disorder). Using the criteria established in the DSM-5 and ICD-10, psychiatric diagnoses are made, and potential treatment options are identified.

Skokauskas et al. [77] has itemized a comprehensive narrative review of studies identifying psychiatric symptoms and diagnoses among children, adolescents, and adults with PWS [77]. From the NIH Rare Disease PWS Registry, the distribution of psychiatric symptoms was determined for 172 participants (62% DEL and 33% UPD and 5% ICD) ranging in age from 8 to 62 years [11, 58]. In the NIH PWS Registry, psychiatric symptoms and their frequencies were reported as follows: depressed mood (30%), anxiety (63%), skin picking (75%), nail picking (46%), compulsive counting (18%), compulsive ordering (42%), plays with strings (19%), visual hallucinations (3%), and delusions (6%) [58]. The Global PWS Registry started to recruit parents of children with PWS in 2015; the 893 participants (47% DEL, 32% UPD, and 3% ICD) have children ranging in age from 8 to 23 years (average age 14 years) [10]. The percentage of respondents that reported the following psychiatric symptoms or diagnoses was as follows: daytime sleepiness (55.8%, 378/677), narcolepsy (12%, 42/349), cataplexy (10.9%, 61/561), seizures (15.7%, 138/880), OCD (87.8%, 452/515), anxiety (54%, 388/718), depression (20%, 143/715), mania (17.6%, 127/723), bipolar disorder (7%, 50/718), psychosis (13.1%, 97/743), and suicidal thoughts (11.6%, 86/744) [71].

Age and genetic subtype are considerations for psychiatric diagnosis in PWS. Young children are more likely to be considered to have ASD, especially among those with UPD, although they may not meet the full criteria [8, 20, 25, 26, 86]. Among 66 children with PWS ages 7–17 years, Lo et al. found that one-third met criteria for ASD [49]. There is a small group of children with UPD who have the full syndrome of ASD; they are nonverbal and low functioning and have high rates of stereotypies [25, 26]. Unlike those with

ASD, these children seek social proximity, and unlike those with PWS, they are not interested in food.

Among young children with PWS, communication disorders are common; language disorder, speech sound disorder, and dysfluency are frequent among DEL, while social communication disorder is more common among UPD [7]. Developmental coordination disorder (motor dyspraxia) occurs frequently. Stereotypic movements or repetitive behaviors are evident, especially with excitement; eye fluttering may be associated with verbal dysfluency. Even among preschool children, tantrums are highly disruptive and may lead to a diagnosis of oppositional defiant disorder. Elimination disorders may occur, such as primary enuresis or problems related to constipation, both of which occur commonly in PWS.

Excessive daytime sleepiness (EDS) is one of the earliest and most enduring diagnostic symptoms seen in PWS from infancy through adulthood. EDS occurred in over half of respondents in the Global Registry [71]. EDS may occur alone or as a result of fragmented sleep due to sleep apnea (obstructive, central, or both) or sleep-related hypoventilation [12]. Fragmented sleep results in night awakenings which may present an opportunity for nighttime foraging for food, and EDS may be a contributing factor to behavioral problems during the daytime. Also, cataplexy and narcolepsy may occur. In the Global Registry, a diagnosis of cataplexy was reported in 11% (61/561 respondents) with a median age of onset of 18 months, predating the onset of narcolepsy, which was reported in 12% (42/349 respondents) with a median age of onset 10 years [71]. Sleep-related seizures, noted to occur between 7 and 9 years of age, were commonly associated with cataplexy and narcolepsy, suggesting a common etiology related to dysfunction in the GABA circuitry [71].

Among school-age children, attention problems, learning difficulties, and social skills deficits may be a focus of evaluation at this time. Processing speed delay, evident during psychiatric evaluation or measured on psychological testing, occurs commonly but not universally in PWS. Processing speed delay interferes with language comprehension and has behavioral consequences. For example, when a child does not respond to a teacher's request in a timely fashion, the teacher may interpret this as oppositional defiance. This alters the teacher's interaction with the child and may increase the child's frustration, which may precipitate a tantrum. Also, processing speed has a substantial impact on communication in group situations with typical peers. By the time an affected child with PWS has understood the topic of conversation with peers and come up with a response, the group has moved on to another topic or another child. This is one of the reasons that children with PWS prefer a dyadic rather than group interaction with peers. Peers with speech and language difficulties may be a better peer group for learning social skills. Otherwise, social isolation and associated psychological ramifications may result.

ADHD is most likely to present as inattentive type, regardless of gender. In fact, a steady increase in symptoms of ADHD was noted among children under 11 years [93], and among 58 children ages 5–18, the prevalence of ADHD was 25% [98]. Disrupted sleep and excessive daytime sleepiness are common and may contribute to symptoms of ADHD; obstructive sleep apnea should always be considered in children with obesity.

The need for sameness leading to ritualistic and repetitive behaviors (e.g., repetitive questioning, difficulty initiating a task, erasing until just right, needing to complete a task before moving on) may interfere with the flow of educational activities in the classroom [33]. Signs of excoriation disorder (skin picking) begin in childhood and increase throughout adolescence and adulthood with a characteristic typology and topography over time [68, 82]; not every study has indicated an increased prevalence in skin picking among DEL versus UPD [40]. Specialized education or schooling is often required for management of learning difficulties, interfering behaviors, and social skills deficits.

Middle school-age children are likely to present with symptoms of anxiety and tantrums. Anxiety increases and peaks between 10 and

14 years [10]. Skokaukas et al. [77] used the CBCL DSM-oriented scales in a cohort of youth with PWS (mean age 9 for boys and 11 for girls) compared to controls and found that "affective problem" was the only domain that had an elevated T-score in the borderline range and only "affective problem" and "somatic problem" were statistically significant compared to controls [77]. Generalized anxiety disorder (DSM-5) is characterized by uncontrolled "apprehensive expectation" together with somatic concerns. Also, there are concentration problems due to being keyed up, irritable, easily fatigued, or having sleep difficulty. Anxiety may predispose to dysthymia, which presents with intermittent low mood or irritability and low self-esteem. Dysthymia (persistent depressive disorder) is a chronic condition associated with misery because the persons cannot predict their mood state from day to day. Impulsive compulsive behaviors are commonplace and may consist of ordering and arranging; lining things up symmetrically; erasing and rewriting for exactness; fixing hygiene sequences, collecting, and hoarding; and completing a set [24, 50, 51, 79]. Repetitive questioning occurs frequently. In the hands of a clinician with PWS experience, rarely do these behaviors meet criteria for a diagnosis of OCD, because they are anxiety binding not anxiety inducing. The child is contented and not distressed when doing them. Further, the phenomenology in PWS differs from typical symptoms of checking, counting, and cleaning seen in OCD [15]. None the less, OCD was diagnosed in 45% of 53 youth in the Shriki-Tal study [72]. Skin picking of variable intensity may be present leading to a diagnosis of excoriation disorder (35% in the Shriki-Tal study); it was less likely to be associated with compulsions [72, 98]. This suggests that although excoriation disorder is listed under obsessive-compulsive-related disorders in DSM-5, it may not be linked with OCD phenomenologically in PWS [39, 96].

Disruptive mood dysregulation disorder (DMDD) presents with irritable mood, and frequent temper outbursts several times per week across at least two settings; there have been no studies on the frequency of this diagnosis in PWS. Disruptive behavior disorder, which includes disruptive, impulse control, and conduct disorders in DSM-5, was the most prevalent psychiatric diagnosis (68% of 53 youth) in this school age group [72]. Lo et al. found that oppositional defiant disorder occurred in 20% of 61 children and adolescents ages 7–17 years, and it was not associated with age [50, 51]. A conduct disorder may be diagnosed if tantrums are associated with intimidation of others, physical fights, cruelty to animals, theft with breaking and entering or confrontation, destruction of property, running away, lack of guilt, remorse, or empathy. Psychotic disorder was diagnosed in 11% of youth [72]. At least one diagnosis was present in 89% of youth, and multiple comorbid diagnoses negatively affected the quality of life [72].

The transition between middle childhood and adolescence is a tumultuous time for youth with PWS. Many parents attribute the intensification of mood and behavioral difficulties to puberty, but biological puberty is delayed in most youth with PWS, so symptoms are not attributable to endogenous hormonal fluctuations. However, this is a time of great psychosocial stress. First, there are increasing demands at school for independent function, which are inconsistent with the environmental controls necessary for safety in PWS. Second, community experience widens, which provides more opportunity to engage in unsafe behaviors. Third, the exposure to typical peers challenges their self-esteem, both academically and in the social hierarchy [95]. Social referencing is common. Most youth become aware that their peers are acquiring secondary sexual characteristics, and they want the same for themselves. Most early adolescents with PWS desire hormone therapy, and most often, it is initiated gradually in females from age 11 years and males from 14 years [60]. But hormone therapy may not be appropriate for those youth who have significant preexisting mood and behavioral problems. Rectal picking and, to a lesser extent, vaginal picking are stress-related behaviors that may become the focus of medical evaluation; they are not masturbatory equivalents [69].

Adolescents with PWS are at risk for stress-related adjustment problems with disturbance of mood and behavior. Most of them are psychologically ill-equipped to negotiate the developmental tasks of adolescence (identity formation, peer networking, intimacy, and vocational planning). Compared to all other age groups, adolescents with PWS are most likely to display externalizing behaviors resulting in disruption of routines, restriction of social activities, and psychological difficulties creating the highest burden of care for parents [45, 54].

There may be cultural differences, however. In Japan, adolescents with DEL ages 13–19 years demonstrated continued gain in social skills and adaptive function, while those with UPD were more likely to show the new onset of symptoms of ASD, especially in the interpersonal (social) and hypersensitivity (sensory) domains [61]. Also, those with UPD displayed the new onset of impulsivity, while inattentiveness did not differ between UPD and DEL, and neither cohort met full criteria for ADHD [61]. These differences associated with genetic subtype continued when comparing adolescents with young adults [42]. And in Taiwan, somatic symptoms in children, adolescents, and young adults (ages 6–23) were the focus of greatest parental distress [99].

Adolescents with PWS are also at risk for depression, which presents with low mood, social withdrawal, loss of interest in pleasurable activities, and changes in sleep or energy level; appetite is a less reliable indicator of mood change. Thought content may reflect low self-esteem, self-depreciation (worthlessness), and feelings of hopelessness or helplessness. Suicidal ideation may be present. Psychosis may occur in the context of depression, and disordered thoughts are mood congruent with paranoid and somatic delusions. Also, bipolar disorder may emerge during adolescence. Hypomania is associated with inflated self-esteem, increased goal-directed behavior, and/or pursuit of activities with high risk for self-harm. All phenotypic behaviors, including food seeking, are increased in hypomania; energy level may be increased, and sleep duration may be decreased. Mania is characterized by psychoses with grandiose delusions. The phenomenology of mood disorders with and without psychosis is discussed in the monograph Mental Health in PWS (https://www.ipwso.org/mental-health-in-pws).

Young adults with PWS continue to experience stress associated with the transition from high school to work with expectations for independent function. Stress levels increase as agency supports shift from school to community and degrees of freedom come into conflict with need for supervision. Emotional maturation is delayed in PWS, and judgment is impaired, regardless of age or IQ. Temper tantrums occur in adulthood and are likely to be diagnosed as intermittent explosive disorder. Anxiety disorders are highly persistent and predispose to mood disorder.

There is an increased risk for mood disorder with or without psychosis in PWS, and there is selectivity with genetic subtype [78]. Persons with deletion are more likely to have depression with or without psychosis with an incidence of 20–30% [75, 78, 91], and persons with maternal uniparental disomy are predisposed to having cyclic psychosis and bipolar I disorder with onset in adolescence and young adulthood, and the incidence increases with age, up to 60% by age 30 years [74, 78, 88, 89, 94]. There has been consideration as to why persons with UPD are neurobiologically predisposed to affective psychosis [1, 52]. All PWS genotypes have an increased incidence of psychosis [6, 9, 14, 53, 90]. Ingasson et al. [41] examined a large population of patients with schizophrenia and schizoaffective disorder and found that the frequency of maternal duplications in the PWS region is a small number but highly correlated with psychosis or autism [41]. Of interest, persons with PWS are likely to lose their interest in food when they are psychotic.

Cyclic psychosis is characterized by sudden onset (not prodromal like schizophrenia), often appearing with confusion like a delirium, associated with intraphasic fluctuations in mood (like rapid cycling bipolar disorder) and accompanied by psychosis with hallucinations and delusions, often with religious themes and

death. It has been associated with motility disturbances and catatonia-like psychomotor phenomena such as dystonia, posturing, stereotypies, mutism, and/or agitation [87]. Cyclic psychosis has a female preponderance. Onset may be associated with stressful life events, duration of symptoms may last up to three months, and recovery is usually associated with return to baseline. Haussman et al. [38] have reviewed the history, phenomenology, and diagnostic criteria for cyclic psychosis [38]. In a retrospective chart review of 10 years of clinical data, Vogels et al. [90] identified 6 out of 59 patients with PWS who experienced a psychotic episode that met the criteria for cyclic psychosis; the onset of illness was between 13 and 19 years; 5 patients had UPD heterodisomy and 1 patient had an IC defect [90]. Soni et al. [78] described this psychiatric illness as an atypical affective disorder and found increased affective disorder among their mothers [78]. Singh et al. [74] found that 11 out of 30 patients with PWS ages 16–34 years met criteria for cyclic psychosis; 4 patients had DEL and 7 had UPD. There was a female preponderance [74].

Among 72 adults with PWS in residential living (51% DEL, 42% UPD), Manzardo et al. [53] identified anxiety disorders (38%), excoriation disorder (33%), intermittent explosive disorder (30%) mostly among males, major depressive disorder (24%) twice as common in females and nearly twice as common among DEL, and bipolar disorder without psychosis (21%) twice as common among UPD. Psychotic features were noted in 23% and were more likely to occur among UPD. There were more psychiatric diagnoses noted among type I than type II DEL [53].

Catatonia is a neuromuscular syndrome that has been known to occur in PWS [18, 19, 28, 66]. It is a psychomotor disorder characterized by stupor or agitation, catalepsy, waxy flexibility, mutism or echolalia, negativism, posturing, mannerisms or echopraxia, stereotypies, or grimacing. It requires prompt medical treatment, has serious consequences, and is likely to reoccur. It is associated with schizophrenia, bipolar disorder, and serious medical problems. Genetic risk for catatonia has been identified inside (*SNORD115*) and outside the critical regions of PWS, with a genetic locus for periodic familial catatonia on chromosome 15q15 [64]. Some researchers now believe that catatonia occurs along a continuum of symptoms with neuroleptic malignant syndrome (NMS), which can be life threatening [34]. The differential diagnosis of catatonia includes catalepsy and cataplexy. Although catalepsy is one of the criteria for catatonia, it may occur independently. It is an involuntary loss of motor function and response to pain with an inability to speak despite being conscious and aware of one's surroundings. Muscle tone is most likely rigid and can be associated with bizarre body postures as seen in catatonia. Breathing and pulse rate can be difficult to detect, and historically people with catalepsy have been thought to be dead! The key difference between catatonia and catalepsy is that in catatonia the person is delirious and not responsive to what is going on in the environment, while in catalepsy, the person is aware but unable to actively respond. Catalepsy has been seen in PWS and has been associated with stress or psychosis. Cataplexy is defined as a sudden and transient loss of muscle tone associated with full conscious awareness. Often, it is associated with strong emotions such as laughing, crying, anger, and terror [65]. Cataplexy is most often associated with narcolepsy, a sleep disorder that has been seen in PWS [92]. But, as previously noted, cataplexy may be present at an earlier age in development than narcolepsy [71].

Because people with PWS are living healthier and longer lives, it is important to discuss the possibility of dementia. There are 40 diagnostic categories covering neurocognitive disorders in the DSM-5, the majority of which are defined by 12 etiologies and designated as minor or major in severity. Each diagnosis is defined by the functional impairment in several cognitive domains: complex attention (attention and processing speed), executive function (planning, decision-making, working memory, error correction, inhibition, and mental flexibility), learning and memory (immediate recall, short-term memory, semantic, autobiographical, and implicit learning), language (receptive and expressive,

e.g.,, naming, word finding, fluency, grammar, and syntax), perceptual motor (visual perception, visual spatial construction, functional motor movement and coordination, recognition of people and objects), and social cognition (recognition of emotions, theory of mind). Of interest, weight loss is a frequently observed problem associated with dementia, independent of pharmacological treatment [32]. Among typical older adults, the incidence of dementia is 1% from age 60 to 65 years, and the number of people diagnosed doubles every 5 years thereafter. When dementia is severe, ADLs are impaired, and supervised living is required. The incidence of dementia in PWS is unknown. However, sporadic cases of dementia with memory impairment and cortical atrophy have been identified [21, 76]. Whittington et al. [97] identified three females aged 45–55 years with UPD who had psychosis and/or bipolar disorder with probable dementia. They experienced a gradual loss of adaptive living skills across domains of semantic language, motor abilities, and social function; they also lost interest in preferred activities and food [97]. Among typical persons, psychosis is a risk factor for later cognitive decline. Thus far, prospective, sequential neuropsychological testing with the Montreal Cognitive Assessment (MoCA) has not provided direct evidence for a dementia-like process occurring among elders with PWS who have had good medical management [21].

The most common type of dementia is Alzheimer's type (AD) with a prevalence approaching 50% by age 85 years in the typical population. Alzheimer's type of dementia is characterized by *short-term memory deficit*. The Mini-Mental State Examination (MMSE) is commonly used for evaluation. AD originates in the hippocampus where working memory is converted to longer memory storage through the action of the neurotransmitter acetylcholine. The neuropathology of AD involves excessive glutamate production and the formation of extraneuronal plaques (amyloid) and intraneuronal tangles (tau) that result in neuronal death. Unfortunately, over a span of 7–10 years, the disease spreads all over the cortex resulting in motor dysfunction that culminates in death. Swaab has reported that he identified some senile plaques in three postmortem brains from PWS, but clinical correlation was unavailable [35]. Medications such as acetylcholinesterase inhibitors (donepezil/aricept) or agents that block formation of glutamate (memantine/namenda) may slow the progression of the disease.

The least common form of dementia is frontotemporal dementia (FTD); it occurs in 1% of the population. The behavioral variant of FTD (bvFTD) is the most pertinent to PWS. Ogura et al. [63] was the first to describe the similarity between the phenotypic behaviors of PWS (food behaviors, stereotypy, and collecting) and the pathological behaviors noted in FTD that emanate from dysfunction in the orbital frontal cortex and anterior temporal lobes [63]. FTD has an earlier age of onset than AD and a more rapid progression. It presents with *personality change*. Memory is intact in these disorders, so the Montreal Cognitive Assessment (MoCA) is used for serial testing instead of the MMSE. The bvFTD is diagnosed by functional neuroimaging such as SPECT scan to identify the part of the brain that is involved. If the dorsolateral prefrontal cortex is affected, an apathy syndrome results with decreased motivation, interest, and curiosity, blunted emotions, lack of spontaneity, neglect of personal hygiene, incontinence, and weight loss due to a decreased desire to eat. It presents like a clinical depression, but it does not respond to antidepressant medication, and stimulants produce restlessness. If the orbital frontal cortex is involved, a disinhibition syndrome results in impulsivity; emotional dyscontrol with irritability, anger, or giddiness; loss of empathy; sexual inappropriateness; food seeking and loss of satiety; and potential for violence or property destruction. There is no pharmacologic treatment for FTD; SSRIs have not been helpful and memantine trials have been equivocal [47]. Environmental management by family and carers is the most effective intervention [56]. Although the phenomenology of bvFTD has many similarities to the PWS phenotype, the evidence to date would not suggest a common neuropathology [31].

Discussion

PWS is caused by the loss of expression of contiguous paternal genes both inside and outside the imprinted region on ch15q11-13. Gene expression is related to the genetic subtype caused by deletion, maternal uniparental disomy 15, or an imprinting center defect. The PWS genotype (DEL, UPD, IC, or others) provides the genetic blueprint that interacts with the normal processes of brain development, experience, and learning to produce lasting effects on the structure and function of the brain. The loss of expression of paternal genes has an enduring impact that interferes with the ability to adapt to the environment both inside and outside the body. A feedback deficit model describes the intrinsic dysfunction in neural and endocrine pathways that create homeostatic dysregulation. In the brain, there is an imbalance in excitatory and inhibitory mechanisms. The deficit in autonomic nervous system regulation is the best example of the complex and dynamic interaction between systemic dysfunction and behavior in PWS. The intrinsic deficits in both sympathetic and parasympathetic tones drive phenotypic behavior to correct the imbalance, but the result cannot be sustained. The behavioral phenotype is the manifestation of this intrinsic, automatic coping strategy driven by the hypothalamus and insula. As such, the neuropsychiatric phenotype of PWS evolves over the course of development; food is just the tip of the iceberg.

In most cases, the characteristic neonatal phenotype leads to genetic testing that confirms the diagnosis soon after birth. Early diagnosis for families is important for initiation of informed and guided management of the syndrome. Optimal nutrition, infant stimulation, and timely initiation of growth hormone (and possibly oxytocin) can lessen the impact of hypotonia and provide an early start toward healthy neurodevelopment in the infant with PWS. During late infancy and early toddler years, there is a window of time when behavior normalizes, especially among those treated with GH. In fact, behavioral testing using the CBCL-T for young children aged 18 months–5 years found that scores for preschool children with PWS were the same as typically developing children except for a mild elevation of the ASD scale [59]. Food-related behaviors aside, developmental persistence of stereotypic behavior, temper tantrums, repetitive restrictive interests, and excessive compulsive behaviors define the PWS phenotype during childhood [39]. These behaviors are more intense in PWS, increase with age, persist throughout young adulthood, and may decrease in middle age. So, the functional manifestation of the underlying neurobiological deficit in PWS may be the failure to assimilate typically emerging behaviors into patterns of adaptive behavior [73]. In a typical person, these behaviors become personality traits; in PWS, they are the domains of the PWS Personality. Figure 23.1 is a schematic of the age of onset, variation in intensity, developmental course, and duration of phenotypic behaviors in PWS.

The neurobehavioral impact of the genetic subtype of PWS becomes apparent from early childhood through the young adult years. Learning problems, intellectual deficiency, speech difficulties, seizures, and compulsive behavior patterns are associated with the presence or absence of the four genes proximal to the imprinted region that differentiate type I from type II deletion. Broadly speaking, the UPD subtype has a bimodal effect on the neuropsychiatric phenotype across development, with features of autistic spectrum and nonverbal communication difficulties appearing in young children and affective psychosis emerging in adolescents and young adults. It is not clear whether those children with features of autistic spectrum are the ones who go on to develop psychosis as adolescents and young adults. However, there may be cultural differences in this paradigm of risk for autism and affective psychosis in UPD. Cross-sectional studies across development from Japan suggest that children with DEL and UPD do not differ in early childhood, but symptoms of autistic spectrum (social withdrawal, selective attention, and impulsivity) emerge during adolescence among UPD, while those with DEL continue to acquire social skills [61]. This difference between genetic subtypes is accentuated in young adults

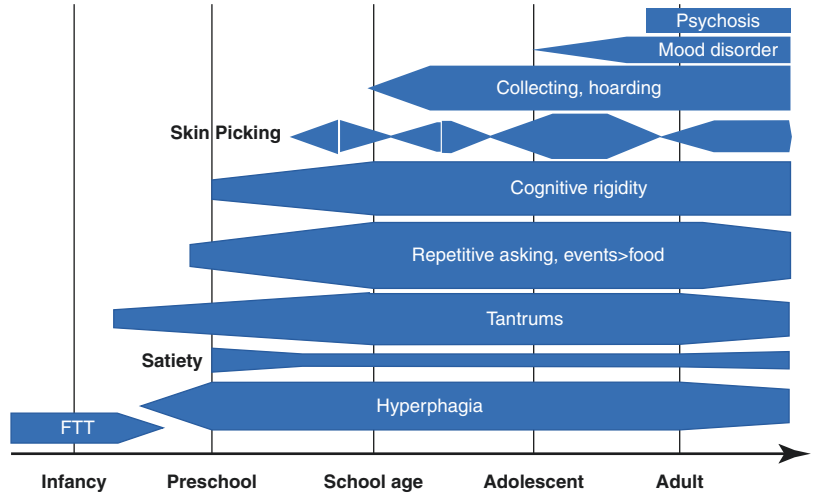

Fig. 23.1 Emergence and progression of behaviors across the developmental life cycle in PWS. Key: FTT, failure to thrive

[42, 62]. The description of acquisition of ASD symptoms in UPD may be consistent with prodromal symptoms of psychosis, although psychosis is not described among these young adults with PWS from Japan. Elsewhere in the literature, there is general agreement that the incidence of psychosis is approximately 60% among those with UPD compared to 11% in DEL, and there are intervening factors that confer both risk and resiliency. Aman has reviewed the factors conferring risk for psychosis including neurophysiological (event-related potentials), genetic, and neurochemical (imbalance between inhibitory GABAergic and excitatory glutamatergic influences) factors [1]. Brain imaging in children and adolescents with PWS found more cortical white matter abnormalities in UPD compared to DEL, similar to the white matter abnormalities seen in typical adolescents with psychotic disorders [52]. Stress sensitivity is probably the most enduring trait in PWS. Because the appearance of severe mental illness is driven by stress, effective stress management during the developmental years and young adult life may have an impact on the age of onset, duration, and recurrence of episodes of severe mental illness in PWS.

Over the past 30 years, there have been many studies examining behavior in PWS and most have been mentioned in this chapter. Because PWS is a rare disease, the early studies included children and adults in the same cohort, and subjects were not distinguished by genetic subtype. Studies have used different assessment tools which make comparisons difficult. There has been no specific pattern of externalizing versus internalizing behaviors over time. Many studies agree that behaviors intensify with age and may diminish after middle age. However, one clinically relevant change over the past 20 years has been the administration of growth hormone. Among infants with PWS, GH therapy improves motor, respiratory, and oral function. Among children with PWS, it normalizes dysphoric facial features and abnormal body composition, improves motor strength and stamina, increases speech and language capability, and improves IQ (abstraction ability). This means that children and youth with PWS who receive GH are more likely to "pass" for typical, and this increases expectations for performance from peers, teachers, and parents. Inevitably, this leads to increased stress, frustration, and disappointment for the person with PWS, resulting in low self-esteem and internalizing behaviors. Although GH is as close to a "magic pill" as possible in PWS, a recent study suggests that it is associated with an increase in anxiety compared to a matched cohort of children and youth who did not receive it [58].

Another clinically relevant change in the management of PWS over time has been the implementation of environmental interventions. The impact of the loss of imprinted genes in PWS confers an inability to adapt to environmental change. There is no question that control of food

access has saved lives, but the implementation of *food security* and family infrastructure in the home has improved quality of life by managing anxiety and behavior. The dissemination of information from PWSA USA, local chapters, and PWS multidisciplinary clinics has helped families implement proper nutrition, daily exercise, and preventative medical care [22]. Early intervention and anticipatory guidance decrease medical comorbidity [46]. Advocacy surrounding school issues and group home placement is essential for families. Finding the classroom environment that best fits the academic, behavioral, and social needs of the child or adolescent is important for stress management as well as enrichment [4]. Similarly, a PWS-specific group home optimizes environmental management for PWS phenotypic behaviors compared to community living arrangements that care for adults with multiple developmental disabilities [67]. An optimal environment decreases anxiety and improves adaptability, which is likely to be reflected on instruments measuring qualitative and quantitative aspects of behavior.

Going forward, a behavioral measure of the PWS phenotype is essential, but it must be sensitive to differences associated with genetic subtype, age, medication, and status of environmental management. This is one of the challenges for future studies that correlate behavior with underlying brain difference in PWS.

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Appendix A: First Published Report of Prader-Willi Syndrome

24

Urs Eiholzer and Phillip D. K. Lee

The first published description of the condition that we now know as Prader-Willi syndrome consisted of a half-page manuscript published in Schweizerische Medizinische Wochenschrift (Swiss Medical Weekly) in 1956, authored by three physicians at University of Zurich: Andrea Prader (1919–2001), Alexis Labhart (1916–1994), and Heinrich Willi (1900–1991) [1]. The completeness and accuracy of their description of the syndrome and its pathophysiological implications are admirable, particularly given the limited diagnostic methods at that time. Their brief manuscript was so comprehensive that no substantial new knowledge regarding the condition was added until the 1980s.

The complete original German-language text of the 1956 article is reprinted here with copyright permission from Swiss Medical Weekly. The article is translated into English by Dr. Urs Eiholzer, who worked with Dr. Prader and is Professor at the University of Zürich and director of the Pädiatrisch Endokrinologisches Zentrum Zürich (Center for Pediatric Endocrinology, PEZZ, Zurich). Dr. Phillip D.K. Lee assisted with editing of the English translation, which has been updated for the current edition of this book (Figs. 24.1, 24.2, and 24.3).

Fig. 24.1 Andrea Prader, 1919–2001

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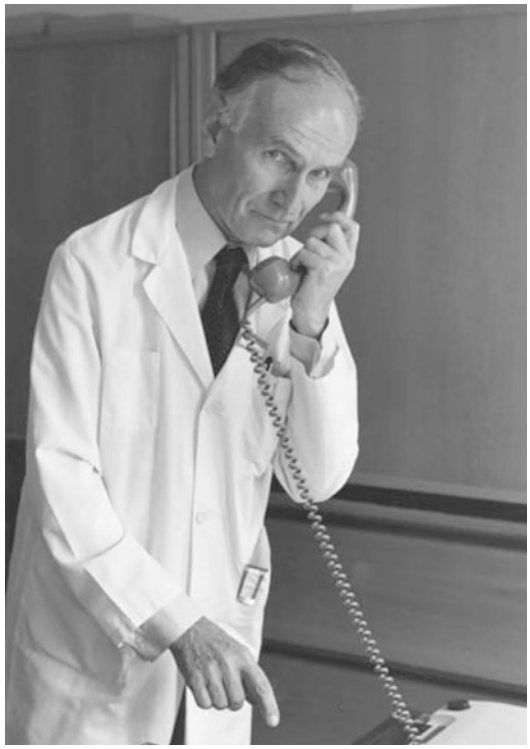

Fig. 24.2 Alexis Labhart, 1916–1994

Fig. 24.3 Heinrich Willi, 1900–1971

Ein Syndrom von Adipositas, Kleinwuchs, Kryptorchismus Und Oligophrenie Nach Myatonieartigem Zustand Im Neugeborenenalter,[1] [1]

A. Prader, A. Labhart, und H. Willi (Universitätskinderklinik, Zürich)

Es handelt sich um ein Syndrom von Kleinwuchs, Akromikrie, Adipositas und Imbezibillität, dem im Säuglingsalter regelmässig eine extrem schwere Muskelhypotonie vorausgegangen ist. Neben variablen kleineren degenerativen Merkmalen findet man beim Knaben regelmässig ein hypoplastisches, flach verstrichenes Skrotum mit inguinaler oder abdominaler Hodenretention.

Bisher haben wir dieses Syndrom bei 5 männlichen und 4 weiblichen Patienten beobachtet. Der älteste Patient ist 23jährig und die älteste Patientin 15jährig. Die übrigen sind 5–10 Jahre alt. Jüngere Patienten haben wir vorläufig nicht miteinbezogen, da sie noch nicht das volle klinische Bild erkennen lassen.

Alle diese Patienten hatten als Neugeborene eine extreme Muskelhypotonie, die sich darin äussert, dass die Kinder fast ganz bewegungslos und schlaff daliegen und weder schreien noch saugen können, so dass einen längere Hospitalisierung notwendig ist. Die Sehnenreflexe sind in diesem Zeitpunkt nicht oder nur schwach auslösbar. Die Diagnose lautet regelmässig “Lebensschwäche” oder “Myatonia congenita”. Nach einigen Wochen macht sich wider Erwarten eine leichte Besserung bemerkbar, doch dauert es Monate, bis die Säuglinge schreien und sich kräftig bewegen können.

Wohl als Folge dieser sich nur ganz allmählich bessernden Muskelhypotonie lernen die Kinder erst mit 1 Jahr sitzen und erst mit 2 Jahren gehen. Während die Hypotonie und Adynamie zusehends bessern, tritt ungefähr um das 2. Jahr die Adipositas auf, und gleichzeitig werden der Wachstumsrückstand und die Oligophrenie deutlich bemerkbar.

Neurologisch findet man nach dem 5. Jahr noch eine geringfügige Muskelhypotonie und eine gewisse motorische Unbeholfenheit, jedoch ein

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normales Reflexbild. Der Kopf ist im Verhältnis zur Körpergrösse eher klein. Im Röntgenbild fehlen signifikante Sellaveränderungen. Die dreimal durchgeführte Luft-und Elektroencephalographie ergab unauffällige Befunde.

Stoffwechseluntersuchungen konnten leider nur bei der Hälfte der Patienten durchgeführt werden. Der Grundumsatz ist normal. Mit Ausnahme des ältesten Patienten, bei dem mit 17 Jahren ein Diabetes mellitus aufgetreten ist, ergibt die Prüfung des KH-, Elektrolyt- und Wasserstoffwechsels mit den üblichen Untersuchungen normale Befunde. Zeichen einer Hypothyreose fehlen. Die Pubertätsentwicklung scheint verzögert und unvollständig zu sein. Die 17-Ketosteroide der älteren Patienten sind auffallend tief. Die Gonadotropinaussscheidung des 23-jährigen Patienten ist erhöht, d.h. es besteht wohl als Folge des Kryptorchismus ein hypergonadotroper Hypogonadismus. Der Vaginalabstrich des 15jährigen Mädchens zeigt eine deutliche Östrogenwirkung. Es scheint also keine Hypophyseninsuffizienz, sondern eher noch eine Hypothalamusstörung vorzuliegen. Bezüglich Ätiologie konnten wir bis jetzt weder für die Heredität noch für eine Embryopathie genügend Anhaltspunkte finden.

Zusammenfassend glauben wir, dass es sich um ein nicht so seltenes, gut abgegrenztes, einheitliches klinisches Syndrom handelt. Beim Säugling und Kleinkind erinnert es an die Myatonia congenita Oppenheim. Im Schulkindalter und später an die Dystrophia adiposogenitalis Fröhlich, an das Laurence-Moon-Biedl-Syndrom und an den hypophysären Zwergwuchs. Trotz mancher Ähnlichkeit lässt es sich aber von allen diesen Syndromen deutlich unterscheiden.

English Translation

A Syndrome Characterized by Obesity, Small Stature, Cryptorchidism, and Oligophrenia Following a Myotonia-Like Status in Infancy

A. Prader, **A. Labhart and H. Willi** (**Zürich Children's Hospital**)

The syndrome is characterized by small stature, acromicria,[2] obesity, and imbecility, preceded by extreme muscle hypotonia in infancy. In addition to variable minor degenerative characteristics, boys are frequently found to have a hypoplastic, flat scrotum with inguinal or abdominal retention of the testicles.

Thus far, we have found this syndrome in five male and four female patients. The oldest patient is 23 years old; the oldest female patient 15 years old. The others are between 5 and 10 years old. For the time being, we have not included younger patients since they do not present with the entire clinical picture.

As neonates, all of these patients suffered from extreme muscle hypotonia; with the children lying almost entirely motionless and floppy, not able to either cry or suck, resulting in prolonged hospitalization. At this stage, tendon reflexes are absent or difficult to elicit. Typically, "congenital myotonia" or debility[3] was diagnosed. Unexpectedly, some improvement was generally seen after several weeks, but it takes months before the infants are able to cry and move with ease.

As a consequence of the slow improvement of muscle hypotonia, the children are only able to sit at 1 year of age and to walk at 2 years of age. While the hypotonia and adynamia[4] gradually improve, obesity sets in around the second year of life. At the same time, growth retardation and oligophrenia[5] become clearly noticeable.

The neurologic findings persist after 5 years of age. Despite muscle hypotonia and some motor clumsiness, reflexes are normal. The size of the head is rather small in relation to body height. X-rays do not reveal any disturbances in the sella[6] area. Pneumo- and electroencephalograms, performed three times, yielded normal results.

Metabolic tests could be conducted in only half of the patients and showed normal basal metabolic rates. Apart from the oldest patient, who had developed diabetes mellitus at 17 years of

[2] Acromicria: small hands and feet.

[3] Lebensschwäche: literally, life-weak; e.g., listless, moribund, debilitated.

[4] Adynamia: lack of physical movement.

[5] Oligophrenia: mental retardation leading to social incompetence, e.g., feeble-mindedness. This term may describe cognitive deficit, which is a major feature of PWS.

[6] Sella *or* sella turcica: the area of the skull that contains the pituitary gland.

age, tests of the carbohydrate, electrolyte, and water metabolism yielded normal results when measured with conventional methods. No signs of hypothyroidism were found. Puberty seems to be delayed and incomplete. In the older patients, measurements of urinary 17-ketosteroid excretion[7] were very low. For the 23-year-old patient, gonadotropin secretion was increased; the cryptorchidism probably led to a hypergonadotropic hypogonadism. The vaginal smear of the 15-year-old girl revealed a distinct effect of estrogens, which makes a hypothalamic disorder more likely than pituitary insufficiency. Regarding etiology, we were not able to find sufficient evidence for heredity or for embryopathy.

In summary, we believe that this syndrome is not all that rare, clearly distinguishable, and well defined. Whereas in infants it shows some similarity to amyotonia congenita of Oppenheim,[8] from school age on and later, it resembles Fröhlich's syndrome (*aka* adiposogenital dystrophy),[9] the Laurence-Moon-Biedl-Bardet syndrome,[10] and pituitary small stature.[11] Despite all the similarities, it can be clearly distinguished from the syndromes mentioned.

[7] 17-ketosteroid excretion: a urinary test for androgen production. This test was commonly used before the development of assays for serum androgens and androgen precursors.

[8] Amyotonia congenita of Oppenheim. In 1900, Dr. Hermann Oppenheim described a clinical condition of severe nonprogressive neonatal hypotonia. Although the term amyotonia congenital of Oppenheim is no longer used, similar symptoms are observed in spinal muscular atrophy and several other congenital neuromuscular conditions [2].

[9] Fröhlich's (*aka* adiposogenital dystrophy) syndrome [3]: This term describes a condition in males with progressively severe obesity associated with hypogonadotropic hypogonadism; the latter usually attributable to a hypophyseal lesion. This term is not commonly used in current medical practice.

[10] Laurence-Moon-Biedl-Bardet syndrome, now more commonly known as Bardet-Biedl syndrome, is characterized by obesity, short stature, moderate mental retardation, retinal dystrophy, polydactyly, and male hypogonadism. More than 20 different genetic abnormalities have been associated with this clinical syndrome [4].

[11] Pituitary short stature: i.e., growth hormone deficiency.

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Appendix B: Comprehensive Team Management of Prader-Willi Syndrome

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Urs Eiholzer and Phillip D. K. Lee

On April 24, 2001, Dr. Urs Eiholzer convened an international meeting of PWS experts in St. Julian's, Malta, to discuss optimal care of individuals with PWS. The meeting was sponsored by the International Prader-Willi Syndrome Organization and funded through a grant from Pharmacia Corporation (which merged with Pfizer Inc in 2003). As a result of the meeting, consensus guidelines were drafted by Dr. Eiholzer and entitled A Comprehensive Team Approach to the Management of Prader-Willi Syndrome. The presenters for the consensus meeting on April 24, 2001, included Urs Eiholzer MD, Margaret Gellatly BSc (Hons), SRD, Phillip D.K. Lee MD, Martin Ritzén MD, and Barbara Y. Whitman PhD. Panelists included Giuseppe Chiumello MD, Yukihiro Hasegawa MD, Priv-Doz Dr med Berthold P. Hauffa, and Maïthé Tauber MD. The guidelines were subsequently revised by Dr. Eiholzer with the assistance of Dr. Phillip D.K. Lee in 2004 and published in Chap. 25 of the previous (3rd) edition of this book [1].

Drs. Eiholzer and Lee have edited, reformatted, and updated the guidelines for the current edition of this book. Additional information regarding the individual recommendations can be found elsewhere in the current edition.

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Overview

Prader-Willi syndrome (PWS) is a complex condition encompassing a range of medical, behavioral, psychiatric, educational, and social concerns. If not adequately treated, the condition is medically devastating for the affected individual typically leading to severe physical disability, with muscle hypotonia, morbid obesity, and consequent medical complications. The social consequences of physical disability are made worse by intrinsic cognitive impairment and behavior abnormalities, leading to impaired social adjustment and limitation of life skills.

Early diagnosis and immediate implementation of treatment have been correlated with improved clinical outcomes. However, despite increased awareness of PWS and typical postnatal signs and symptoms, many individuals with PWS are not diagnosed in infancy. In addition, treatment is often delivered in an uncoordinated and piecemeal manner by healthcare providers who are not experienced with the condition.

The incidence of PWS is estimated to be approximately 1 in 20,000–25,000 live births, and there is an increased age-related mortality. The resulting low prevalence of PWS has limited

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the development of single-center comprehensive PWS clinics to medical centers in more populous urban areas. For individuals with PWS, frequent visits to such a center may not be feasible due to distance, cost, and other factors. Nonetheless, such centers can provide experienced guidance and intermittent assessment of treatment effectiveness for the care of individuals with PWS.

The guidelines presented in this Appendix provide a framework for achieving and maintaining comprehensive multidisciplinary care for individuals with PWS, enabling continuity between the single-site comprehensive centers and delivery of care by community practitioners. It is our recommendation that all individuals with PWS receive their initial assessment in a PWS-focused clinic and that individuals with PWS be assessed in a PWS-focused clinic at least annually. A PWS-focused clinic refers to a clinic directed by a physician with a specialized clinical interest in PWS, with availability of appropriate ancillary services as described below. Our recommendations are similar but not identical to other published multidisciplinary care recommendations for individuals with PWS [2–4].

Care Team

A PWS-focused clinic should include the following individuals:

- Medical director: A PWS-focused clinic should be directed by a physician with specialized PWS-related clinical experience and expertise. The medical director provides leadership of the clinical services, maintains current standard-of-care practice, and provides overall coordination of care. The medical director for a PWS-focused clinic is often an endocrinologist or geneticist.
- Specialty nurse or medical assistant who assists the medical director with maintaining the treatment plan for each patient during and between visits.

Additional professionals should be available for as-needed consultation either in the PWS-focused clinic or as an ancillary service:

- Geneticist.
- Endocrinologist.
- Dietitian.
- Therapists: physical therapist, occupational therapist, speech therapist.
- Behavior specialist, usually a psychologist or psychiatrist.
- Education specialist (this service may be provided by the behavioral specialist or occupational therapist).
- Social worker.

Other clinical subspecialty services should be available for consultation: orthopedist, gastroenterologist, ophthalmologist, urologist, cardiologist, and gynecologist.

Ideally, all healthcare professionals should have knowledge and experience regarding the natural history and current standard of care for individuals with PWS.

Sequential Care

Based on the natural history of PWS, the following sequence of medical care can be constructed. The PRN (pro re nata) ongoing management refers to services recommended by the medical director of a PWS-focused clinic.

	Ideal timing	Team member(s)	Ongoing management
Diagnosis and genetic counseling	Neonate	(Neonatologist) Geneticist	PRN
Assessment of psychosocial situation and resources	Upon confirmation of diagnosis	Social worker	PRN
Endocrine assessment and GH treatment	As soon as possible after confirmation of diagnosis Pre-treatment assessment may include confirmation of normal thyroid status and GH/IGF axis evaluation, as clinically indicated	Endocrinologist	Every 3–6 months
Cryptorchidism and micropenis: evaluation and treatment	Neonate, if clinically indicated	Endocrinologist Urologist	PRN
Feeding therapy, dietary counseling	Neonate	Dietitian Occupational therapist Gastroenterologist, if clinically indicated	PRN, with routine assessments if clinically indicated
Neuromotor developmental assessment and therapy	By 1 month old	Physical and occupational therapists	PRN, with routine assessments if clinically indicated
Speech assessment and therapy	By 12 months old	Speech therapist	PRN, with routine assessments if clinically indicated
Dental care	By 12 months old	Dentist	Annual and PRN
Scoliosis screen	By 12 months old and as clinically indicated	Medical director Orthopedist, if clinically indicated	Scoliosis exam should be performed at least annually Imaging studies PRN
Behavioral assessment and counseling	By 12 months old	Behavioral specialist or psychologist Psychiatrist, as needed	Annual and PRN
Educational assessment and counseling	3–4 years old	Educational specialist	Annual and PRN
Screening for diabetes mellitus and dyslipidemia	Should be considered in obese patients, particularly after 10 years old	Endocrinologist	PRN
Assessment of gonadal function and consideration of gonadal steroid treatment	At 13–15 years old for males and 11–13 years old for females	Endocrinologist	Annual and PRN
Osteoporosis screening	~14–15 years old (earlier if clinically indicated)	Endocrinologist	PRN dual X-ray absorptiometry (DEXA) scan; usually not more than annually
Transition to adult GH treatment	At completion of height growth: approximately 17 years old for males and 15 years old for females	Endocrinologist	Every 3–6 months
Other adult health concerns	After 18 years old	Cardiologist Gynecologist	Annual and PRN
Consideration of adult living options	After 18 years old	Social worker	PRN

Diagnosis and Genetic Counseling

The therapeutic importance of diagnosing PWS in the neonatal period is well recognized [5, 6]. In principle, recognition of PWS during the neonatal period should be straightforward since virtually all newborns with PWS present with characteristic signs and symptoms related to severe hypotonia. In addition, pregnancies in which the fetus has PWS are often complicated by decreased fetal movement and polyhydramnios. Most neonates with PWS require prolonged hospitalization, usually in a neonatal intensive care unit, and specialized nutrition, including parenteral and/or enteral feeding. Given the widespread availability of genetic testing for PWS, diagnostic testing should be considered for all neonates with unexplained hypotonia and weak suck [7, 8]. Nonetheless, many individuals with PWS are not diagnosed until long after infancy.

To address the issue of delayed diagnosis and treatment, inclusion of PWS testing in routine newborn screening programs and in prenatal testing has been proposed. However, until such screening is widely available, PWS care teams can play a significant role in educating neonatologists and other healthcare providers to recognize the typical signs and symptoms.

After confirmation of diagnosis, genetic counseling should be performed, preferably by a geneticist or genetic counselor who is familiar with the natural history of PWS. Periodic genetic evaluation and counseling may occur to update parents or other caretakers regarding advances in our understanding of PWS.

Psychosocial Assessment

Management of an individual with PWS can impose significant ongoing challenges for parents and other family members [9]. Initial and annual assessment of the living situation, financial resources, and other aspects of daily life can greatly enhance the ability to cope with the associated stress and to utilize social and community resources.

Endocrine Assessment and Initiation of GH Treatment

Recombinant human growth hormone (GH; somatropin and biosimilars), which received regulatory approval for treatment of PWS in the USA and the European Union in 2000 and shortly thereafter in other countries, continues to be the only approved treatment for PWS.

GH treatment of PWS starting in infancy or early childhood reproducibly leads to marked improvement in growth and, perhaps more importantly, muscle tone and function. Anecdotal experience suggests additional positive effects on speech development and cognitive functioning particularly in children treated with GH starting in infancy, although these effects may be at least partly secondary to the improvement in muscle function.

Clinical monitoring of childhood GH treatment is recommended at 3–6-month intervals for assessment of medication compliance, clinical response, and need for dose adjustment. Pubertal assessment should also be conducted during these visits, particularly starting in late childhood, given the potential risks for premature adrenarche and central precocious puberty.

Evaluation of Cryptorchidism and Micropenis

Cryptorchidism, usually bilateral, occurs in most infant males with PWS, and a significant proportion have micropenis. Evaluation of cryptorchidism in early infancy permits functional testing based on testosterone level, taking advantage of the physiologic mini puberty. Functional assessment of testicular function in later infancy or childhood requires a cumbersome gonadotropin stimulation procedure. If micropenis is present and a decision is for low-dose testosterone treatment, this is best undertaken in infancy.

Feeding Therapy and Dietary Counseling

The typical natural history of PWS is poor feeding due to hypotonia in infancy, often requiring prolonged parenteral or enteral nutrition, followed by an unusually uncontrollable hyperphagia as muscle function improves, allowing the child to request and acquire food independently. This hyperphagia results in abnormal preferential increase in body fat, resulting in progressive obesity without parallel increase in muscle mass and function.

This typical natural history is significantly modified with childhood GH treatment. Children treated with GH starting in early infancy may have a shorter time period for requiring nutritional support. In addition, GH improves acquisition of nonfat mass resulting in a proportion of fat to lean mass that is closer to that observed in non-PWS populations. However, the degree to which GH treatment alters feeding behavior and risk for obesity is variable, and individuals with PWS continue to have the same population risk for obesity even in the absence of PWS-specific hyperphagia. Obesity continues to be a major contributor to morbidity and mortality in PWS.

Dietary assessment and counseling are required to maintain adequate nutritional intake while avoiding excessive gain of fat mass, considering both PWS-specific and non-PWS-related eating behavior. Adequacy of calcium and protein intake should also be targeted.

Other Therapies: Physical, Occupational, and Speech

Several studies have demonstrated the positive benefits of physical and occupational therapies on neuromotor development in infants and children with PWS and continued positive benefit on muscle strength and function in older children and adults with PWS.

Delayed speech and speech impediments are common in PWS, related to both neuromotor function and cognitive delay. In infancy, speech and feeding therapies are often closely linked. Later in infancy and through childhood, speech therapy should be coordinated with physical and occupational therapies.

Scoliosis Screen

Scoliosis is frequently observed in PWS and in some cases may be observed in utero or at birth, indicating a congenital rather than acquired condition. The pathogenesis is likely neuromuscular, e.g., related to hypotonia, rather than due to intrinsic vertebral abnormalities or tissue malformation. Examination of back curvature should be performed at birth and at least annually, with radiographic studies and orthopedic evaluation as clinically indicated.

Behavioral (or Psychological) and Educational Assessments and Counseling

Cognitive disability is a major feature of PWS. Failure to recognize and appropriately address cognitive disability can significantly hinder intellectual development and contribute to behavioral issues. PWS-specific behavioral assessment should start in infancy and continue thereafter in coordination with other therapies. Teachers and school systems may not be aware of the unique features of PWS; guidance provided by the PWS care team can greatly enhance the educational experience for a child with PWS.

Behavioral counseling should also address peer relationships, dating, and sexual relationships (including precautions) as appropriate for age.

Some individuals with PWS manifest signs and symptoms of psychiatric disorder ranging from attention deficit disorder to schizophrenia. For these cases, referral to a psychiatrist should be made, preferably to a psychiatrist who has experience with individuals who have PWS.

Screening for Diabetes and Dyslipidemia

There is no PWS-specific risk for diabetes mellitus or lipid disorders. Nonetheless, screening for prediabetes/diabetes and dyslipidemia should be considered starting in late childhood, with earlier screening if clinically indicated, in patients with obesity or positive family history of diabetes, dyslipidemia, or early atherosclerotic heart disease.

Gonadal Function and Treatment

There has also been increasing recognition of a need for judicious gonadal steroid replacement in most young adult males and a proportion of females with PWS. In males with PWS, experience suggests that testosterone replacement should be initiated at a biologically appropriate time, i.e., in early adolescence.

Bone Density Measurement

Clinically significant low bone mineral density is not a usual finding in children with PWS. However, children with PWS may be at risk for low calcium intake and low vitamin D levels for variety of reasons; vitamin D levels may be checked intermittently.

Starting in the second decade of life, individuals with PWS may have increased risk for osteoporosis related to hypogonadism. Monitoring of bone mineral density by dual X-ray absorptiometry should be considered, particularly if there is clinical evidence for hypogonadism and gonadal steroid replacement is delayed or refused.

Transition to Adult Growth Hormone Treatment

Beneficial effects of GH treatment have been documented in adults with PWS, who also frequently have abnormally low levels of insulin-like growth factor I (IGF-I) and growth hormone. Since height growth can be used for treatment monitoring, growth hormone treatment of adults is often targeted to maintain IGF-I within a selected normal range.

Documentation of adult growth hormone deficiency, accompanied by low insulin-like growth factor I (IGF-I) level, may be required by some medical coverage programs, particularly in the USA. For these cases, any ongoing childhood growth hormone treatment must be discontinued, IGF-I levels should be monitored at 6-month intervals, and growth hormone testing considered when the IGF-I level is judged to be sufficiently low.

If documentation of adult growth hormone treatment is not required, then any ongoing growth hormone treatment can be lowered to the usual lower end of the adult dose range and then adjusted to maintain IGF-I levels within the desired range.

Similar procedures can be used for adults with PWS who are naïve to GH treatment or who have been off treatment.

Other Adult Health Concerns

In addition to continuation of PWS-related health and psychologic concerns, adults with PWS will require usual age-related health maintenance, which may include gynecologic exams, diabetes and cancer screening, and cardiology evaluation. Continued periodic evaluation in a comprehensive PWS clinic is recommended, with coordination of other healthcare needs by the team or by the primary care physician.

Consideration of Adult Living Options

Even before there was focused attention on comprehensive care, most adults with PWS were employed and able to live semi-independently. With comprehensive care, including physical improvements due to growth hormone treatment, lifestyle options and opportunities have expanded. The social worker in the comprehensive care

team can provide ongoing guidance regarding semi-independent residential facilities, educational and employment opportunities, and community resources.

The Late-Diagnosed or Late-Treated Individual with PWS

Individuals with PWS who are diagnosed and/or receive initial treatment (especially growth hormone treatment) after childhood will likely retain much of the classic PWS phenotype, including the typical hyperphagia, obesity, and hypotonia even with treatment. For these patients, comprehensive team management is essential for assessment and management of PWS-specific treatment needs.

Final Comments

PWS is an uncommon, uniquely complex, multisystem condition which is best managed by an experienced multidisciplinary comprehensive care team [10, 11]. Maximum treatment benefit is realized if diagnosis and implementation of multidisciplinary treatment occurs in the neonatal period.

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Appendix C: Growth Charts of Individuals with Prader-Willi Syndrome

26

Merlin G. Butler

Data from the United States

Data in Figs. 26.1, 26.2, 26.3, 26.4, and 26.5 are based on measurements of 71 Caucasian US subjects with PWS between the ages of 0 and 24 years, including 42 males and 29 females, reported by Butler and Meaney (1991). Under high-resolution chromosome analysis, 37 subjects had an apparent chromosome 15 deletion, 26 had normal-appearing chromosomes, and 8 had an unknown chromosome status. Approximately half of the subjects were on a calorie-restricted diet, and none were treated with growth hormone. No significant differences were found between those with a chromosome deletion and those with normal-appearing chromosomes, but there were significant variations by gender.

Data source: Butler MG, Meaney FJ. Standards for selected anthropometric measurements in Prader-Willi syndrome. *Pediatrics*. 1991;88(4):853–60. (Reproduced by permission of *Pediatrics*, 1991;88:853–8. Charts were modified by Dr. Merlin Butler to add standard measure equivalents to the original metric units.)

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https://doi.org/10.1007/978-3-030-98171-6_26

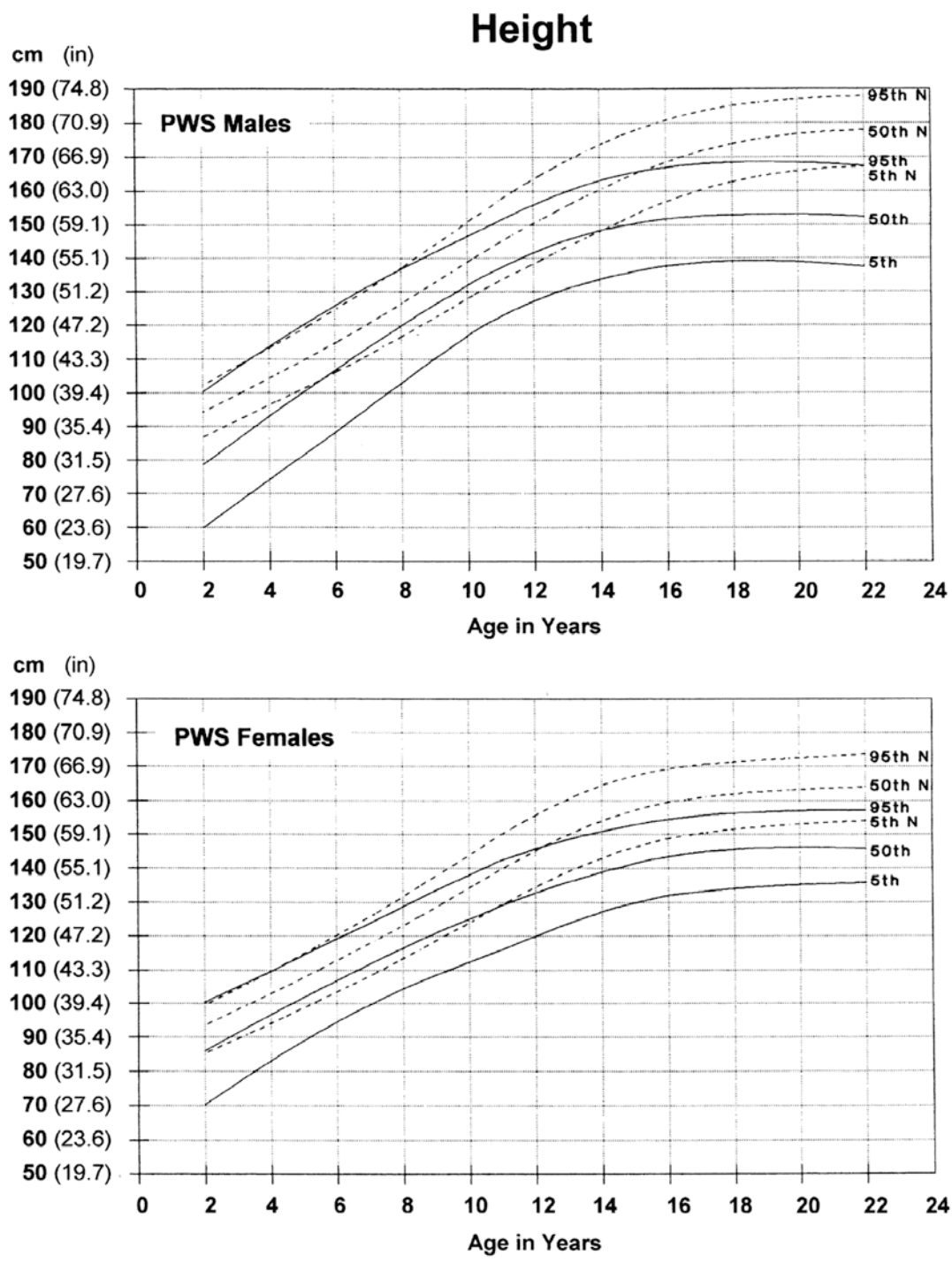

Fig. 26.1 Data from the United States. Standardized curves with percentiles for height of male and female patients (solid line) with Prader-Willi syndrome (PWS) and healthy individuals (broken line). (Modified from Butler and Meaney (1991). Reproduced by permission of *Pediatrics*, Vol. 88, p. 854, Copyright © 1991)

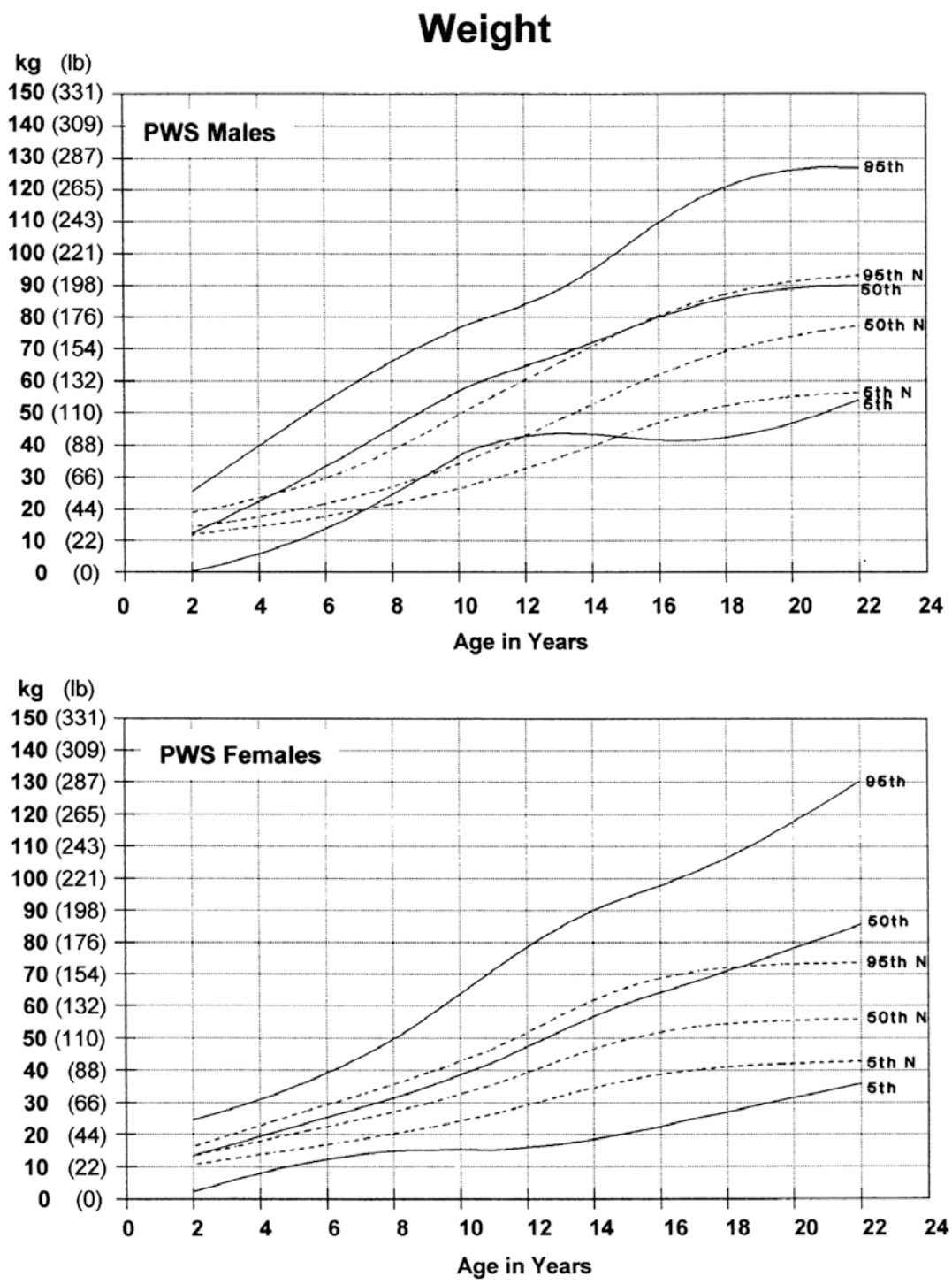

Fig. 26.2 Data from the United States. Standardized curves with percentiles for weight of male and female patients (solid line) with Prader-Willi syndrome (PWS) and healthy individuals (broken line). (Modified from Butler and Meaney (1991). Reproduced by permission of *Pediatrics*, Vol. 88, p. 853, Copyright © 1991)

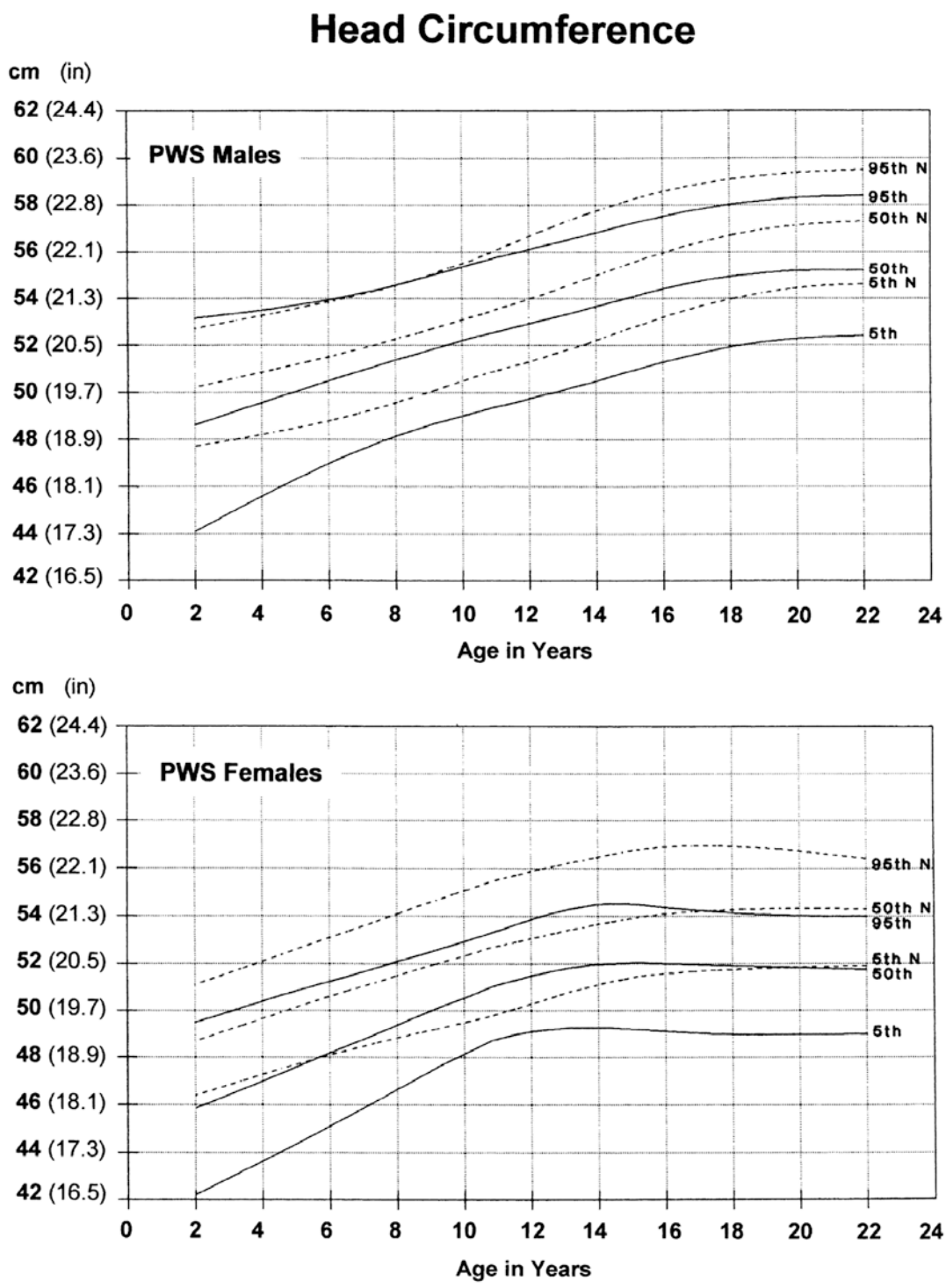

Fig. 26.3 Data from the United States. Standardized curves with percentiles for head circumference of male and female patients (solid line) with Prader-Willi syndrome (PWS) and healthy individuals (broken line). (Modified from Butler and Meaney (1991). Reproduced by permission of *Pediatrics*, Vol. 88, p. 855, Copyright © 1991)

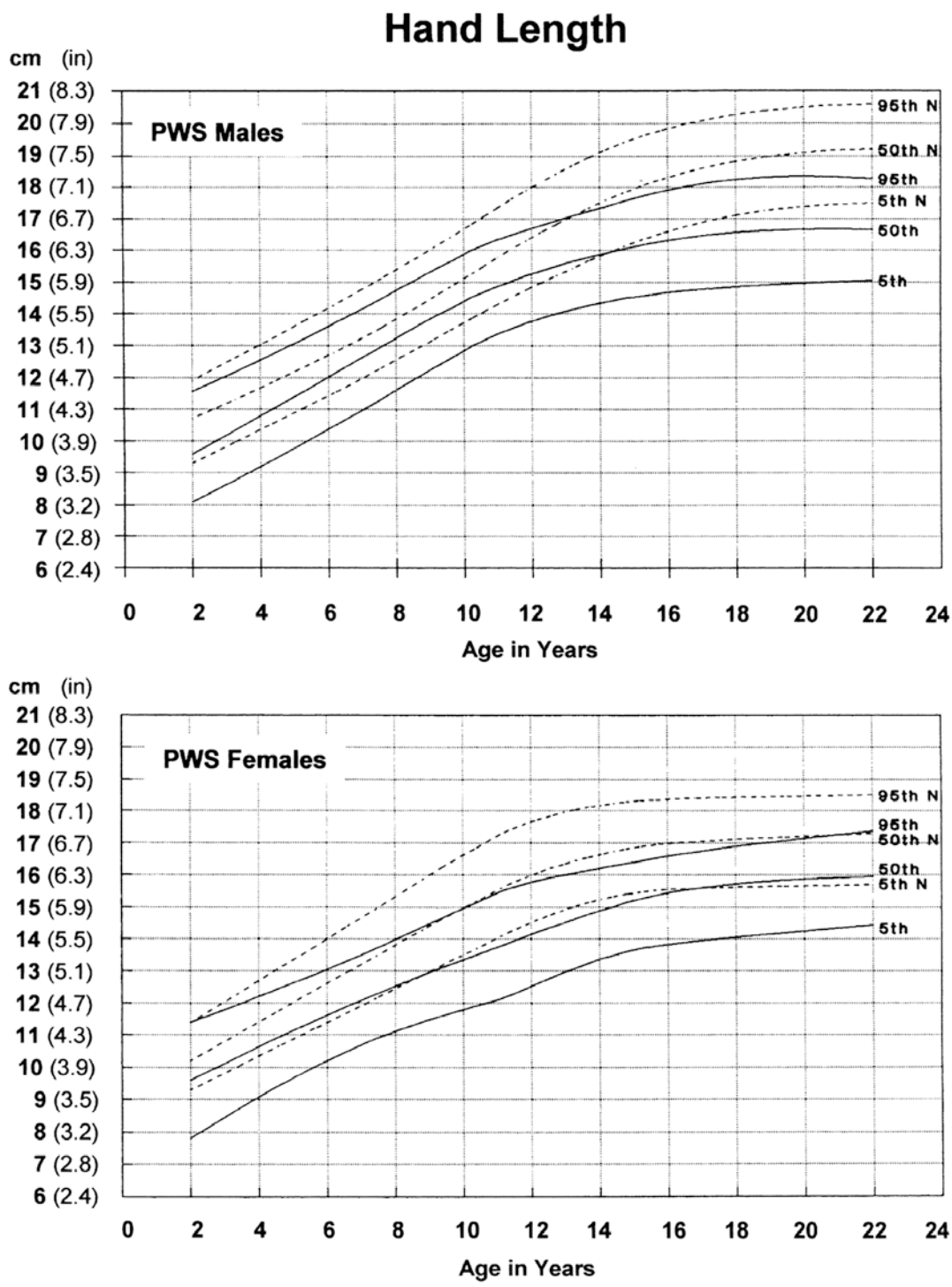

Fig. 26.4 Data from the United States. Standardized curves with percentiles for hand length of male and female patients (solid line) with Prader-Willi syndrome (PWS) and healthy individuals (broken line). (Modified from Butler and Meaney (1991). Reproduced by permission of *Pediatrics*, Vol. 88, p. 856, Copyright © 1991)

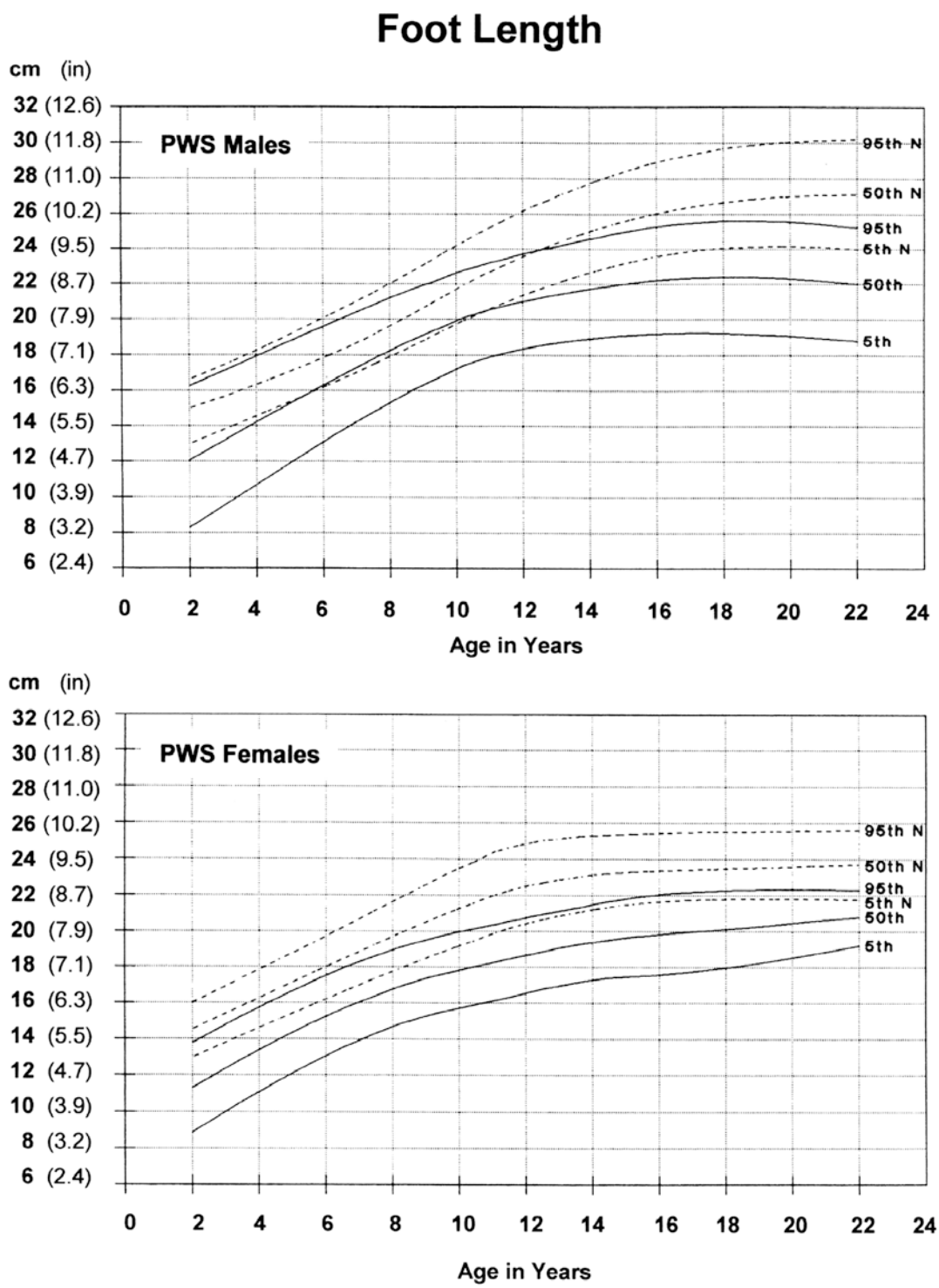

Fig. 26.5 Data from the United States. Standardized curves with percentiles for foot length of male and female patients (solid line) with Prader-Willi syndrome (PWS) and healthy individuals (broken line). (Modified from Butler and Meaney (1991). Reproduced by permission of *Pediatrics*, Vol. 88, p. 858, Copyright © 1991)

Data in Figs. 26.6, 26.7, 26.8, 26.9, and 26.10 were based on measurements from 186 non-growth hormone treated white infants (108 boys and 78 girls) representing the genetic subtypes with PWS between 0 and 36 months of age reported by Butler et al. (2011) with the normative 50th percentile plotted on each standardized infant growth curve. The goal was to monitor growth and compare data with other infants with PWS. No significant differences in growth measures were seen when comparing data among the infants (boys or girls) with PWS having 15q11-q13 deletion or maternal disomy 15.

Data source: Butler MG, Sturich, J, Lee, J, Myers, SE, Whitman, BY et al. Growth standards of infants with Prader-Willi syndrome. *Pediatrics*. 2011;127:687–95.

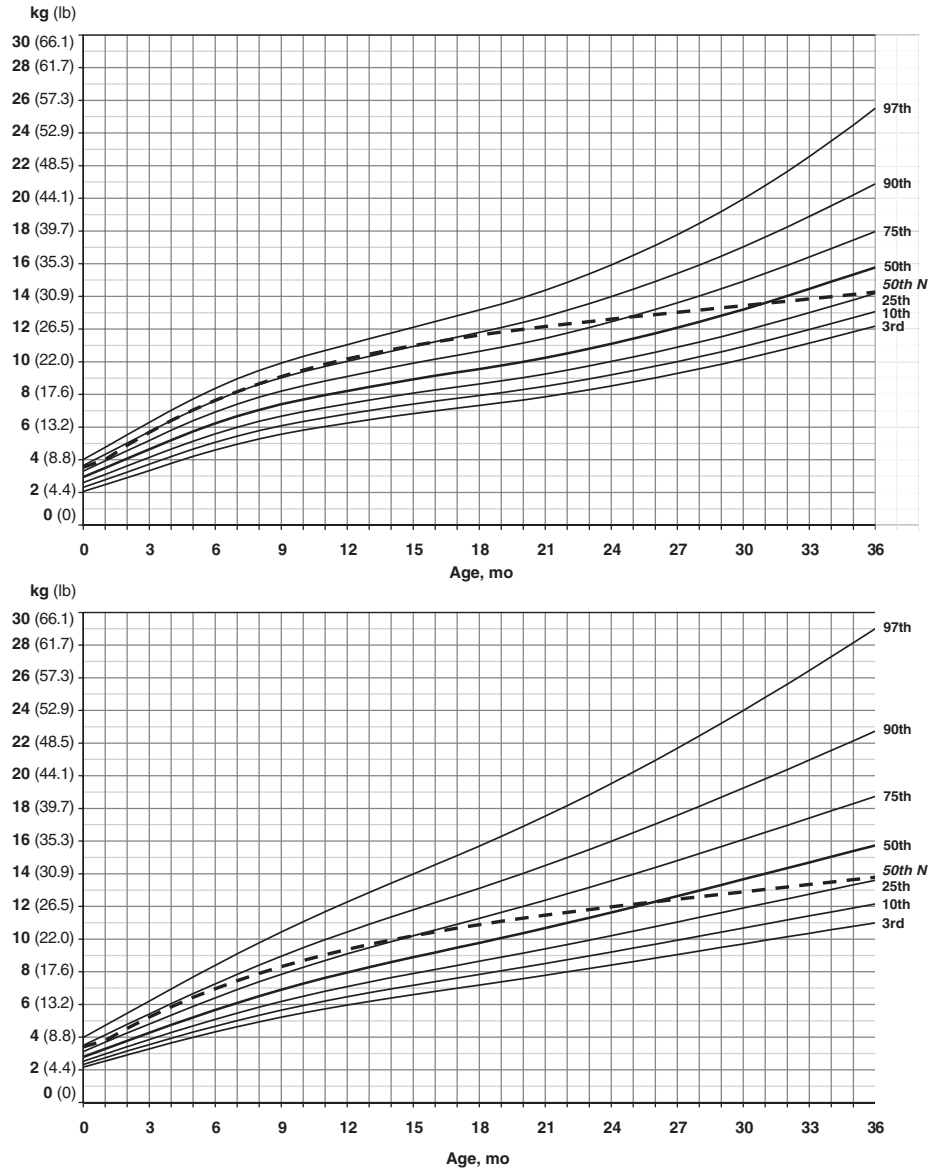

Fig. 26.6 Standardized curves for weight of male (upper) and female (lower) infants with PWS without growth hormone treatment (solid lines) and normative 50th percentile (broken line) without growth hormone treatment. (Reprinted with permission from Butler MG, et al. Growth standards of infants with Prader-Willi syndrome. *Pediatrics*. 2011;127:687–95)

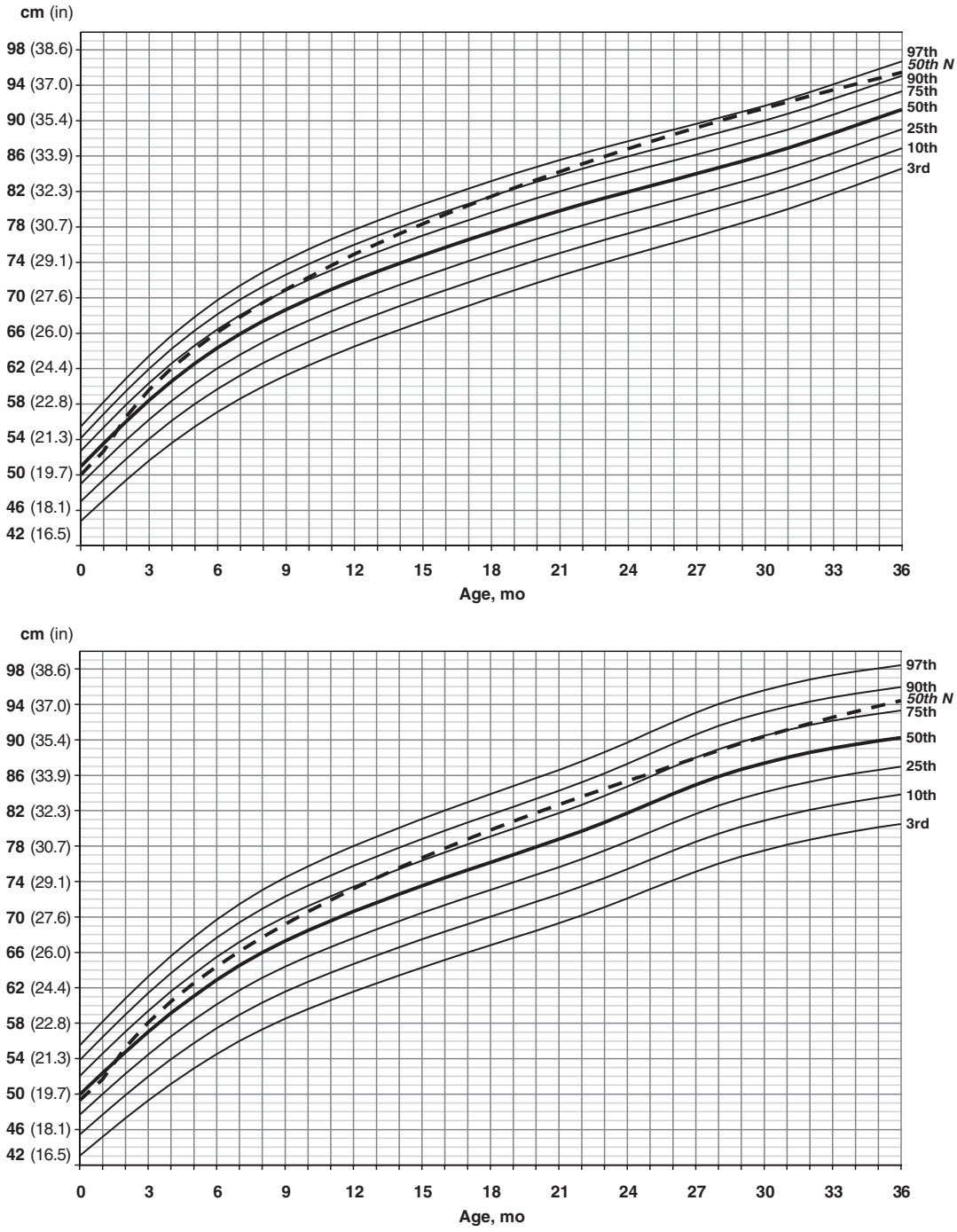

Fig. 26.7 Standardized curves for length of male (upper) and female (lower) infants with PWS without growth hormone treatment (solid lines) and normative 50th percentile (broken line) without growth hormone treatment. (Reprinted with permission from Butler MG, et al. Growth standards of infants with Prader-Willi syndrome. *Pediatrics*. 2011;127:687–95)

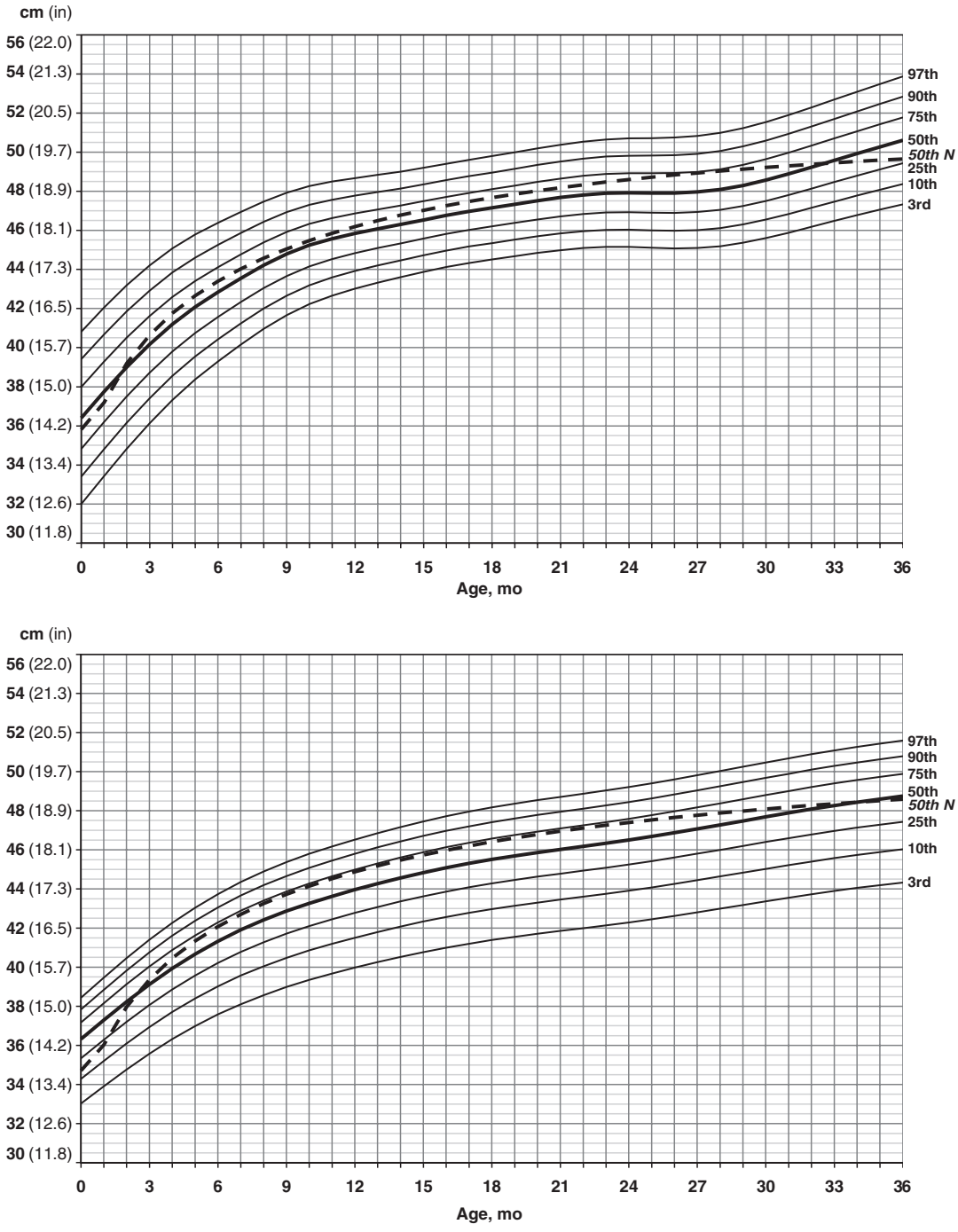

Fig. 26.8 Standardized curves for head circumference of male (upper) and female (lower) infants with PWS without growth hormone treatment (solid lines) and normative 50th percentile (broken line). (Reprinted with permission from Butler MG, et al. Growth standards of infants with Prader-Willi syndrome. *Pediatrics*. 2011;127:687–95)

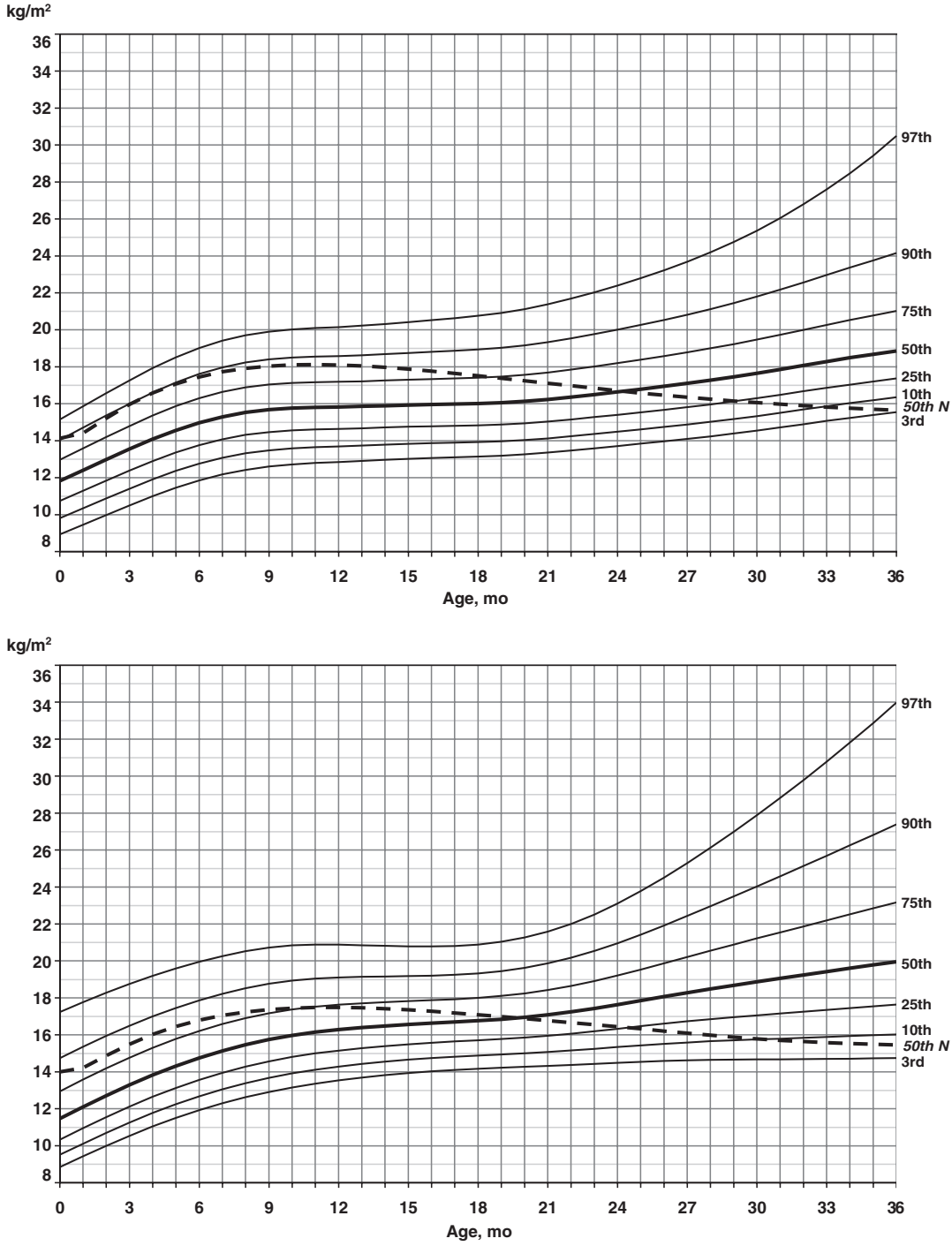

Fig. 26.9 Standardized curves for BMI of male (upper) and female (lower) infants with PWS (solid lines) and normative 50th percentile (broken line) without growth hormone treatment. (Reprinted with permission from Butler MG, et al. Growth standards of infants with Prader-Willi syndrome. *Pediatrics*. 2011;127:687–95)

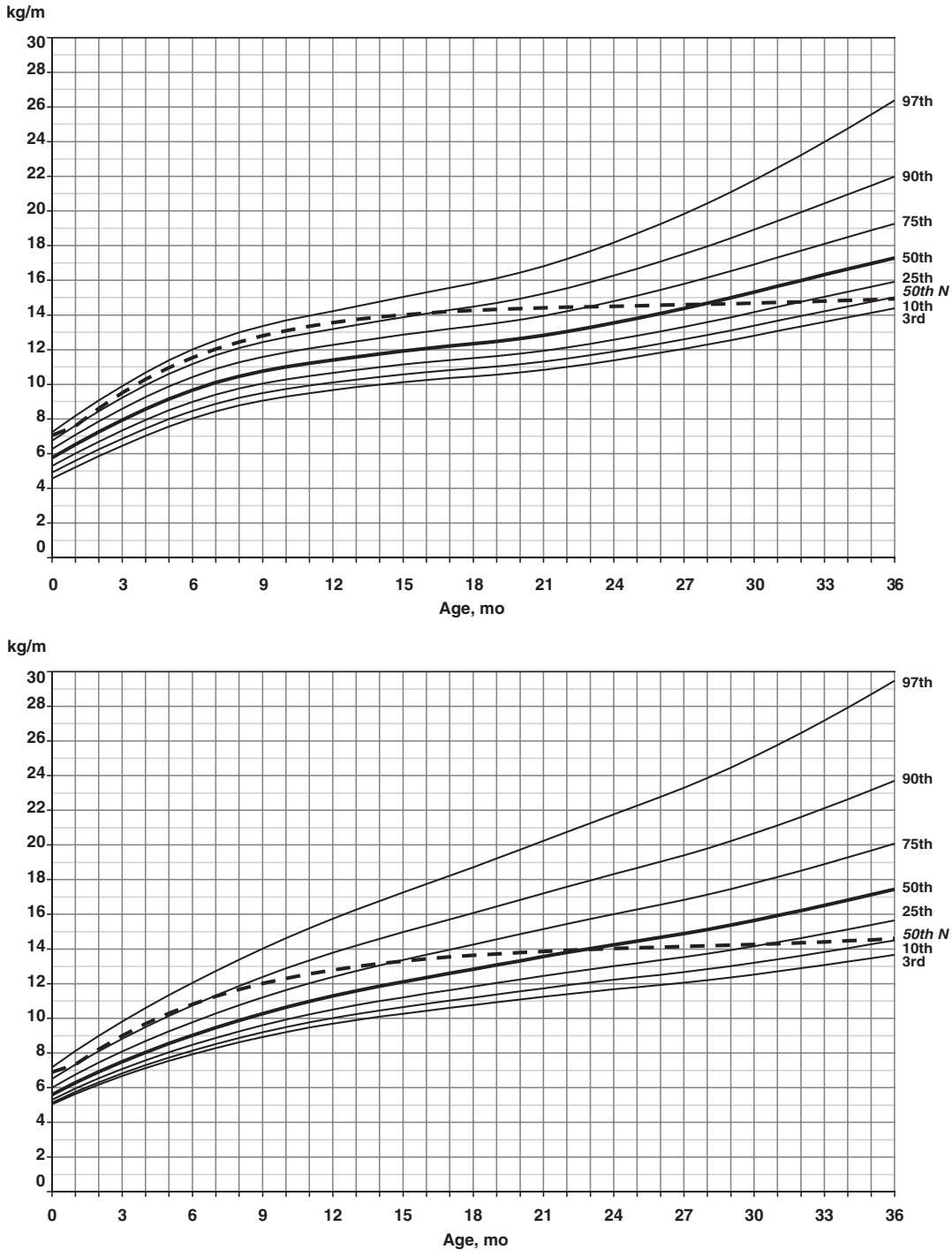

Fig. 26.10 Standardized curves for weight/length of male (upper) and female (lower) infants with PWS without growth hormone treatment (solid line) and normative 50th percentile (broken line). (Reprinted with permission from Butler MG, et al. Growth standards of infants with Prader-Willi syndrome. *Pediatrics*. 2011;127:687–95)

Data in Figs. 26.11, 26.12, 26.13, and 26.14 were based on measurements from 120 non-growth hormone treated white subjects (63 males and 57 females) with PWS representing the genetic subtypes between 3 and 18 years of age reported by Butler et al. (2015). Standardized growth charts were developed for the 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles for weight, height, head circumference, and BMI along with comparison with normative growth patterns.

Data source: Butler MG, Lee, J, Manzardo, A, Gold J, Miller, J et al. Growth charts for non-growth hormone treated Prader-Willi syndrome. *Pediatrics*. 2015;135:e126–35.

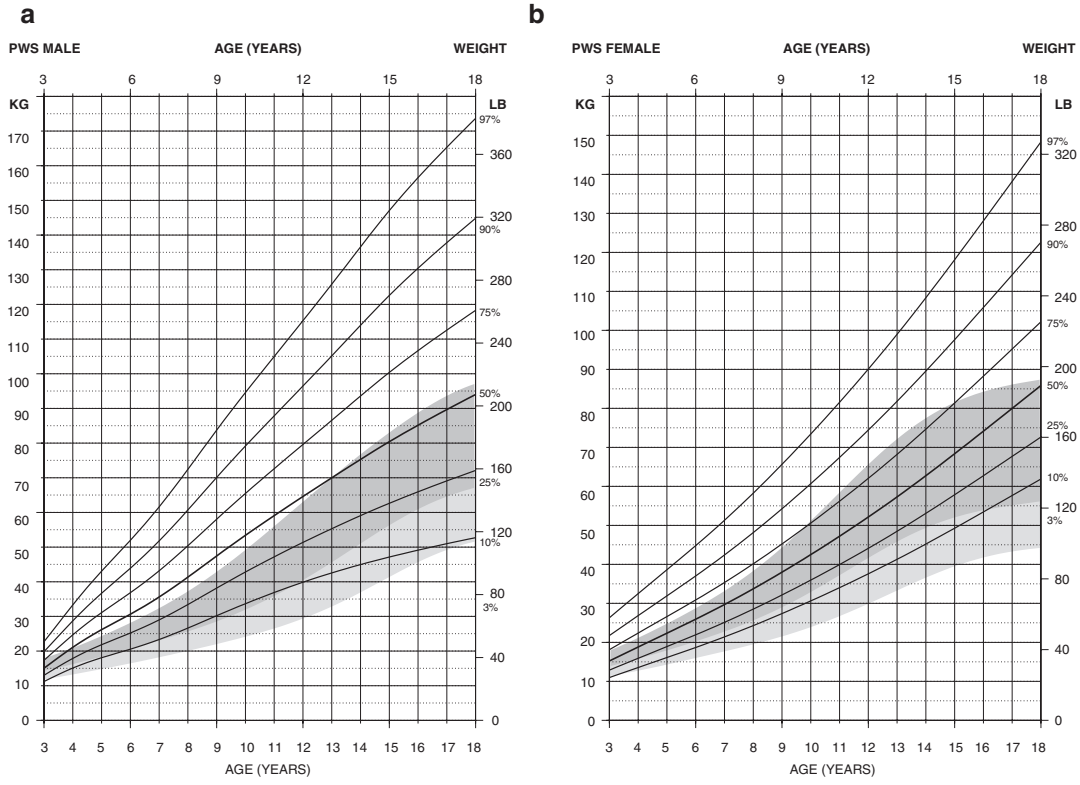

Fig. 26.11 Standardized curves for weight of non–growth hormone–treated subjects (male subjects (left) and female subjects (right)) with PWS (solid lines) and normative percentile ranges (shaded area) with normative 97th to 50th percentiles in dark shading and 50th to 3rd percentiles in light shading. (Reprinted with permission from Butler MG, et al. Growth charts for non-growth hormone treated Prader-Willi syndrome. *Pediatrics*. 2015;135:126–35)

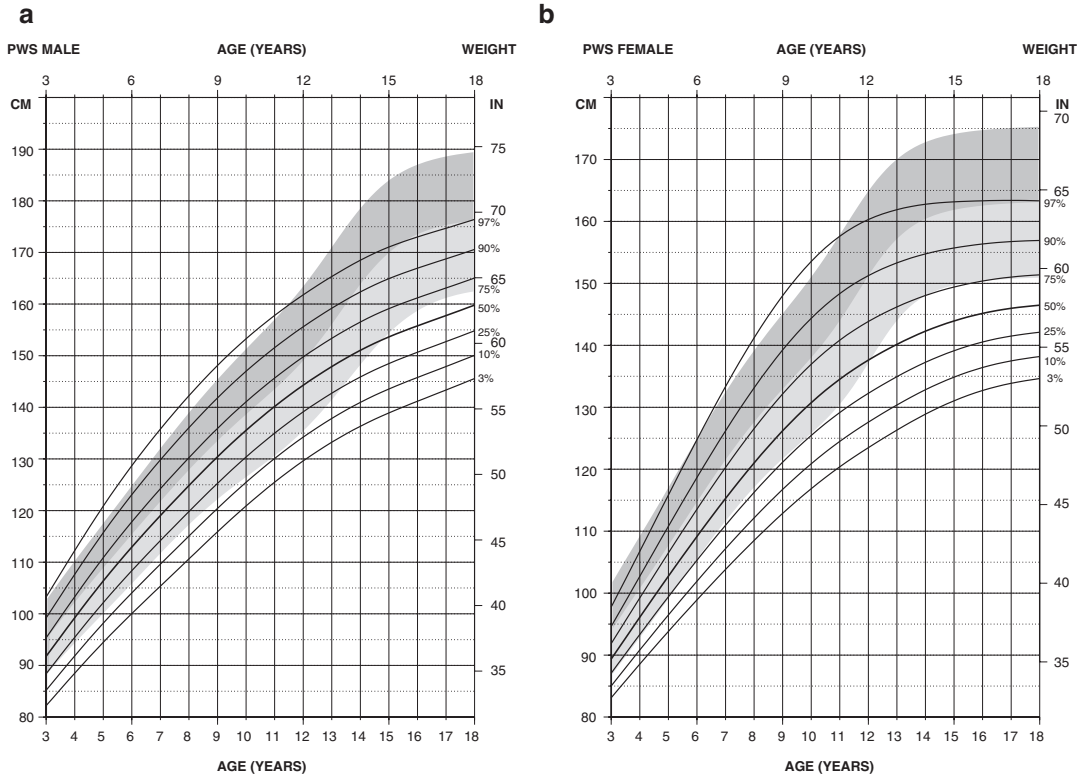

Fig. 26.12 Standardized curves for height of non–growth hormone–treated subjects (male subjects (left) and female subjects (right)) with PWS (solid lines) and normative percentile ranges (shaded area) with normative 97th to 50th percentiles in dark shading and 50th to 3rd percentiles in light shading. (Reprinted with permission from Butler MG, et al. Growth charts for non-growth hormone treated Prader-Willi syndrome. *Pediatrics*. 2015;135:126–35)

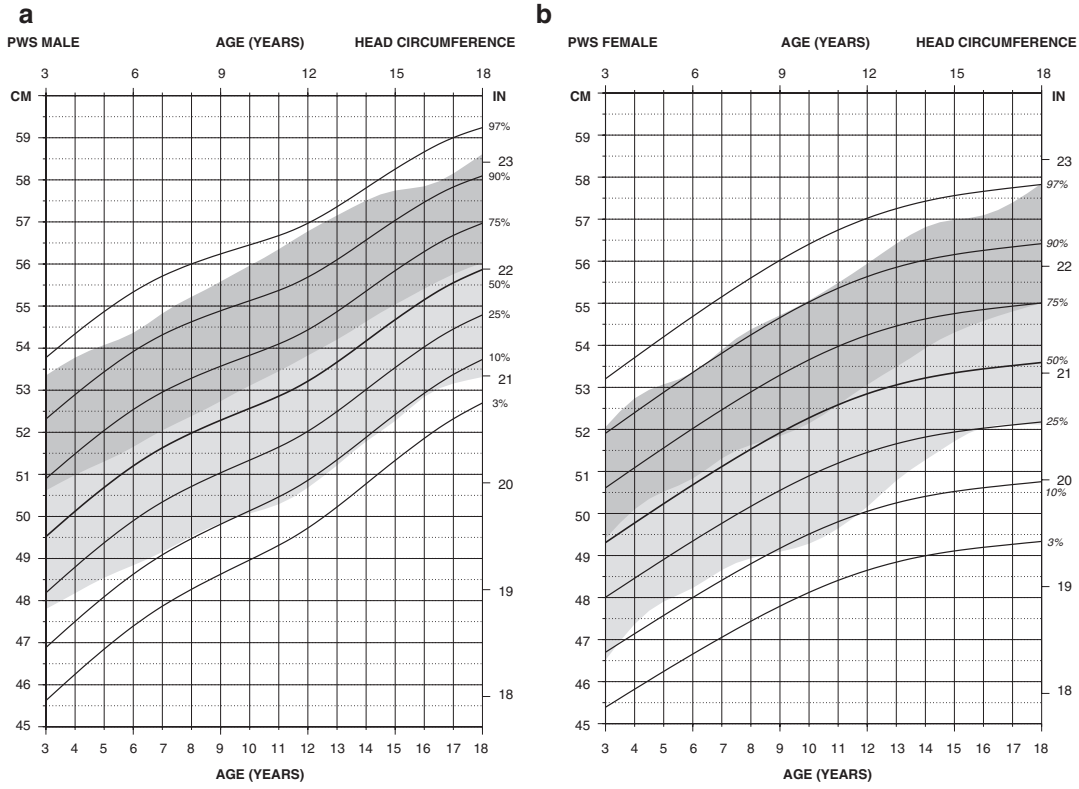

Fig. 26.13 Standardized curves for head circumference of non–growth hormone–treated subjects (male subjects (left) and female subjects (right)) with PWS (solid lines) and normative percentile ranges (shaded area) with normative 97th to 50th percentiles in dark shading and 50th to 3rd percentiles in light shading. (Reprinted with permission from Butler MG, et al. Growth charts for non-growth hormone treated Prader-Willi syndrome. *Pediatrics*. 2015;135:126–35)

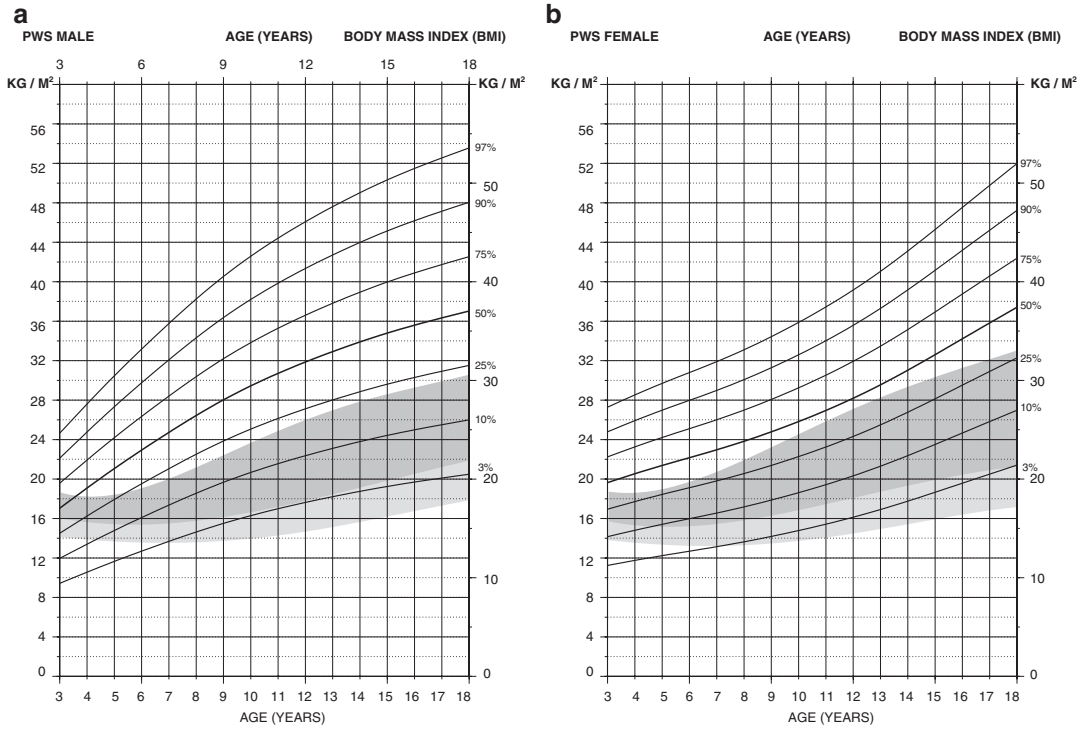

Fig. 26.14 Standardized curves for BMI weight of non–growth hormone–treated subjects (male subjects (left) and female subjects (right)) with PWS (solid lines) and normative percentile ranges (shaded area) with normative 97th to 50th percentiles in dark shading and 50th to 3rd percentiles in light shading. (Reprinted with permission from Butler MG, et al. Growth charts for non-growth hormone treated Prader-Willi syndrome. *Pediatrics*. 2015;135:126–35)

Data in Figs. 26.15, 26.16, 26.17, and 26.18 were based on measurements obtained from 171 subjects (78 males and 93 females) with PWS representing the genetic subtypes and reported by Butler et al. (2016). They were treated with growth hormone for at least 40% of their lifespan between 0 and 18 years of age. Most were enrolled between 2003 and 2013. Growth hormone treatment was determined by measuring IGF-1 levels at recommended regular intervals. They had no history of scoliosis. PWS-standardized growth curves were developed for seven percentile ranges and compared with normative 3rd, 50th, and 97th percentiles. Growth hormone treatment appeared to normalize stature and markedly improved weight in PWS compared with standardized curves for non-growth hormone treated individuals with PWS.

Data source: Butler MG, Lee J, Cox DM, Manzardo A, Gold J, et al. Growth charts for Prader-Willi syndrome during growth hormone treatment. *Clin Pediatr (Phila).* 2016;55:957–74.

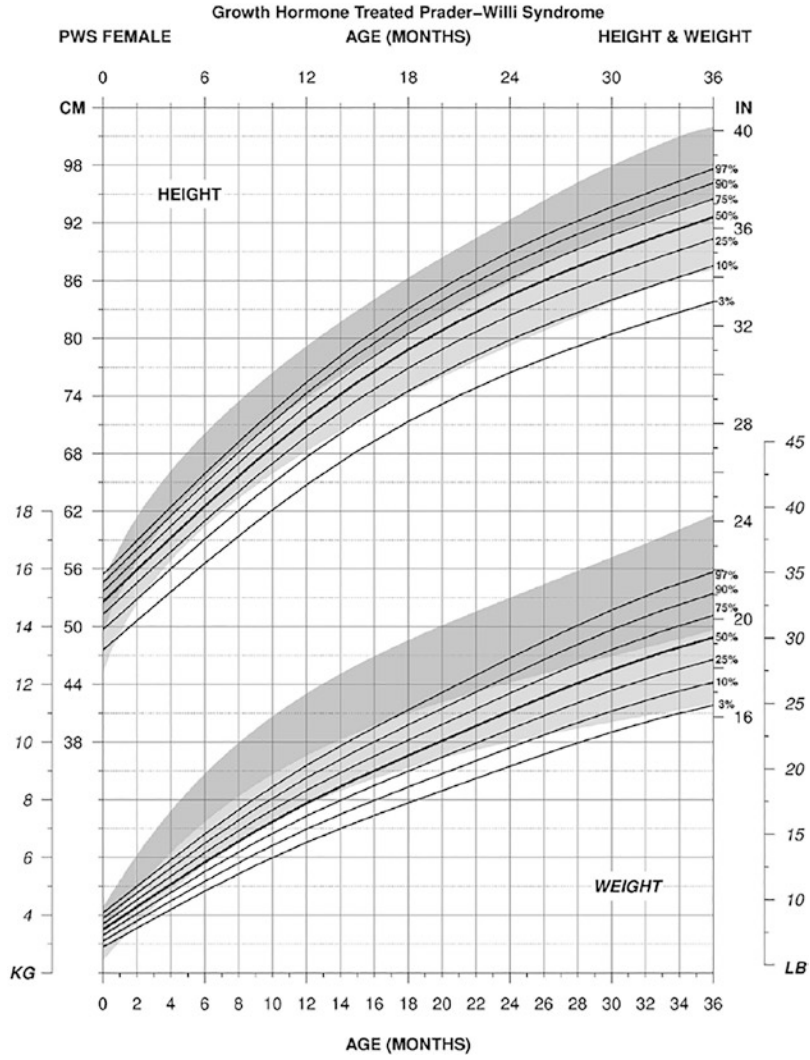

Fig. 26.15 Standardized curves for height (upper) and weight (lower) from birth to 3 years of age for growth hormone–treated females with Prader-Willi syndrome (solid lines) and normative percentile ranges (shaded area) with normative 97th to 50th percentiles in dark shade and normative 50th to 3rd percentiles in light shade. (Reprinted with permission from Butler MG, et al. Growth charts for Prader-Willi syndrome during growth hormone treatment. *Clin Pediatr*. 2016;55:957–74)

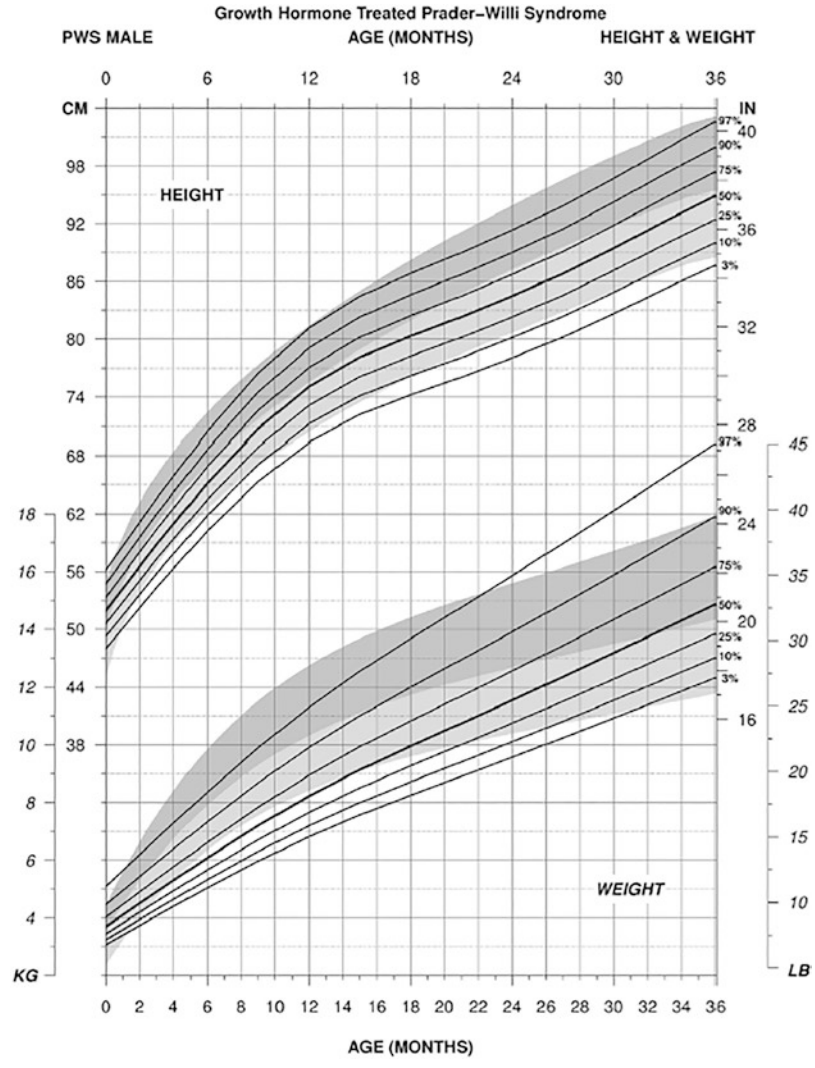

Fig. 26.16
Standardized curves for height (upper) and weight (lower) from birth to 3 years of age for growth hormone–treated males with Prader-Willi syndrome (solid lines) and normative percentile ranges (shaded area) with normative 97th to 50th percentiles in dark shade and normative 50th to 3rd percentiles in light shade. (Reprinted with permission from Butler MG, et al. Growth charts for Prader-Willi syndrome during growth hormone treatment. *Clin Pediatr*. 2016;55:957–74)

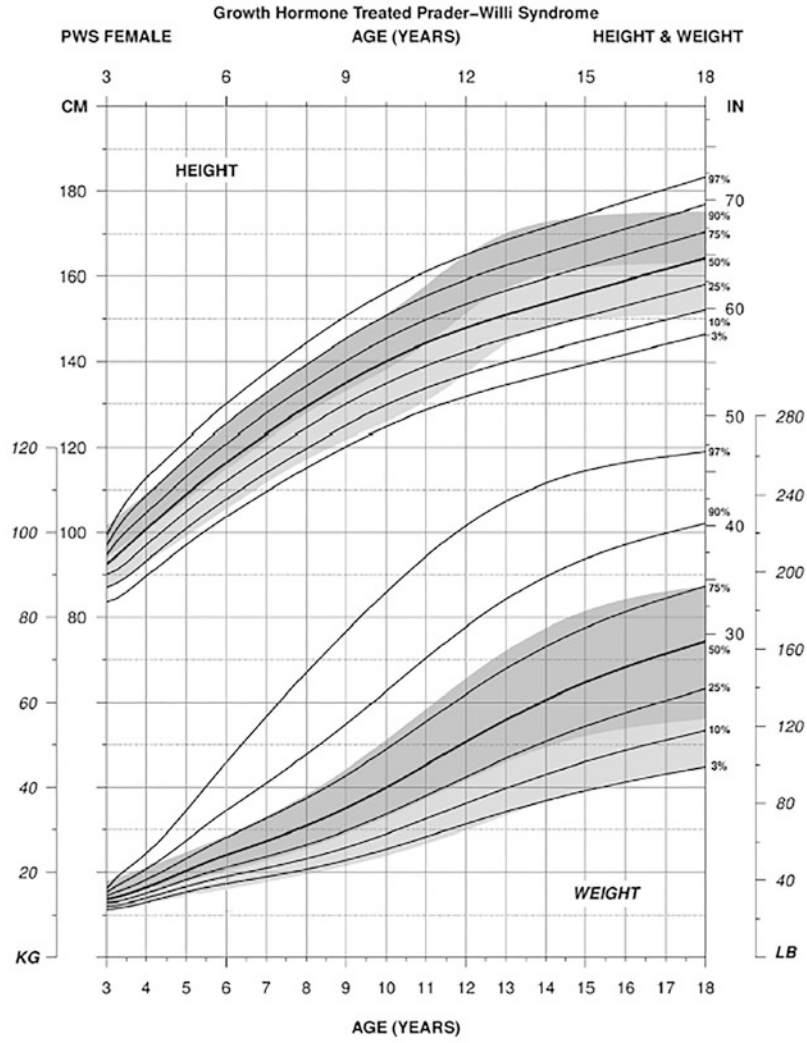

Fig. 26.17
Standardized curves for height (upper) and weight (lower) from 3 to 18 years of age for growth hormone–treated females with Prader-Willi syndrome (solid lines) and normative percentile ranges (shaded area) with normative 97th to 50th percentiles in dark shade and normative 50th to 3rd percentiles in light shade. (Reprinted with permission from Butler MG, et al. Growth charts for Prader-Willi syndrome during growth hormone treatment. *Clin Pediatr*. 2016;55:957–74)

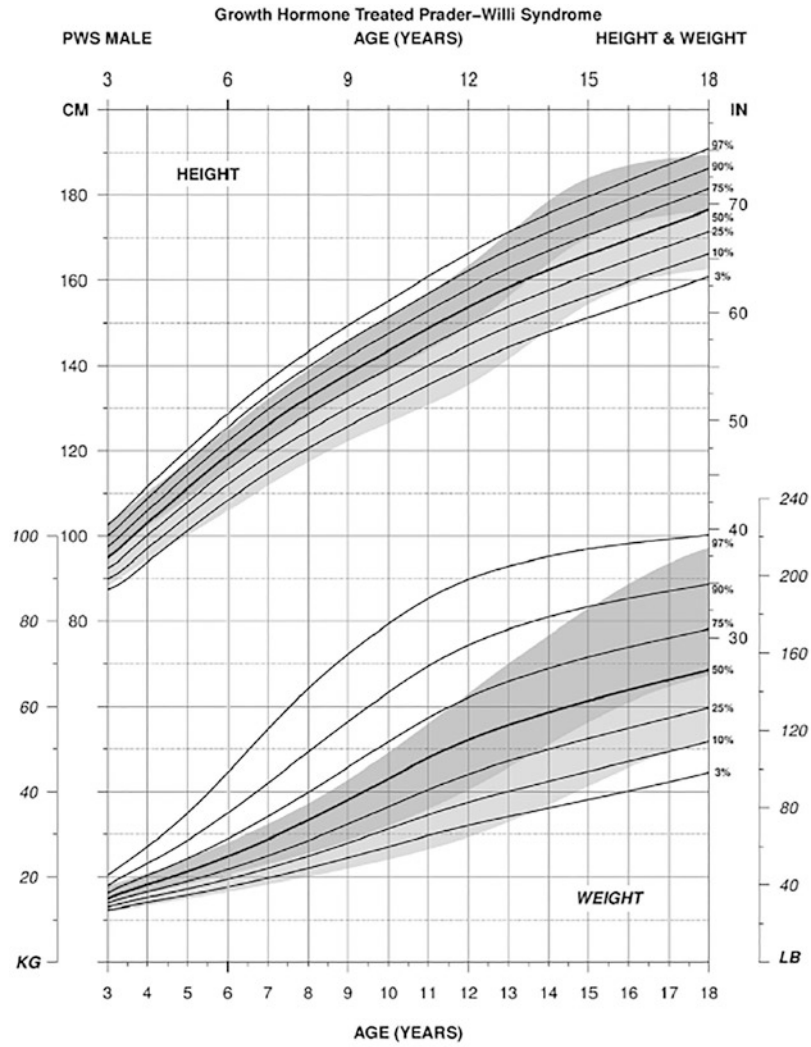

Fig. 26.18 Standardized curves for height (upper) and weight (lower) from 3 to 18 years of age for growth hormone–treated males with Prader-Willi syndrome (solid lines) and normative percentile ranges (shaded area) with normative 97th to 50th percentiles in dark shade and normative 50th to 3rd percentiles in light shade. (Reprinted with permission from Butler MG, et al. Growth charts for Prader-Willi syndrome during growth hormone treatment. *Clin Pediatr*. 2016;55:957–74)

Data from Germany

Data in Figs. 26.19 and 26.20 are based on measurements of 100 subjects of German descent between the ages of 0 and 20 years, including 51 males and 49 females, reported by Hauffa et al. All subjects had genetically confirmed PWS by molecular genetics testing; 76 had deletions, 14 had maternal uniparental disomy, 3 had imprinting mutations, and 7 were of undetermined molecular class. None of the subjects had received a growth-promoting therapy. In comparison with the US data described above, the researchers found that "Height centile curves of the German patients fall in the tall range of standards derived from American patients … mainly due to an elevation of the lower centile ranges in both sexes." They also found that after age 14, "German girls with PWS are heavier than their American counterparts."

Data source: Dr. Berthold P. Hauffa provided combination height and weight charts based on PWS data reported in Hauffa BP, Schlippe G, Roos M, Gillessen-Kaesbach G, Gasser T. Spontaneous growth in German children and adolescents with genetically confirmed Prader-Willi syndrome. *Acta Paediatr*. 2000;89:1302–11. These modified clinical charts were prepared by Pharmacia Corporation, substituting German reference data for the Dutch reference data in the original article. Reprinted with English labels by permission of Pharmacia Corporation.

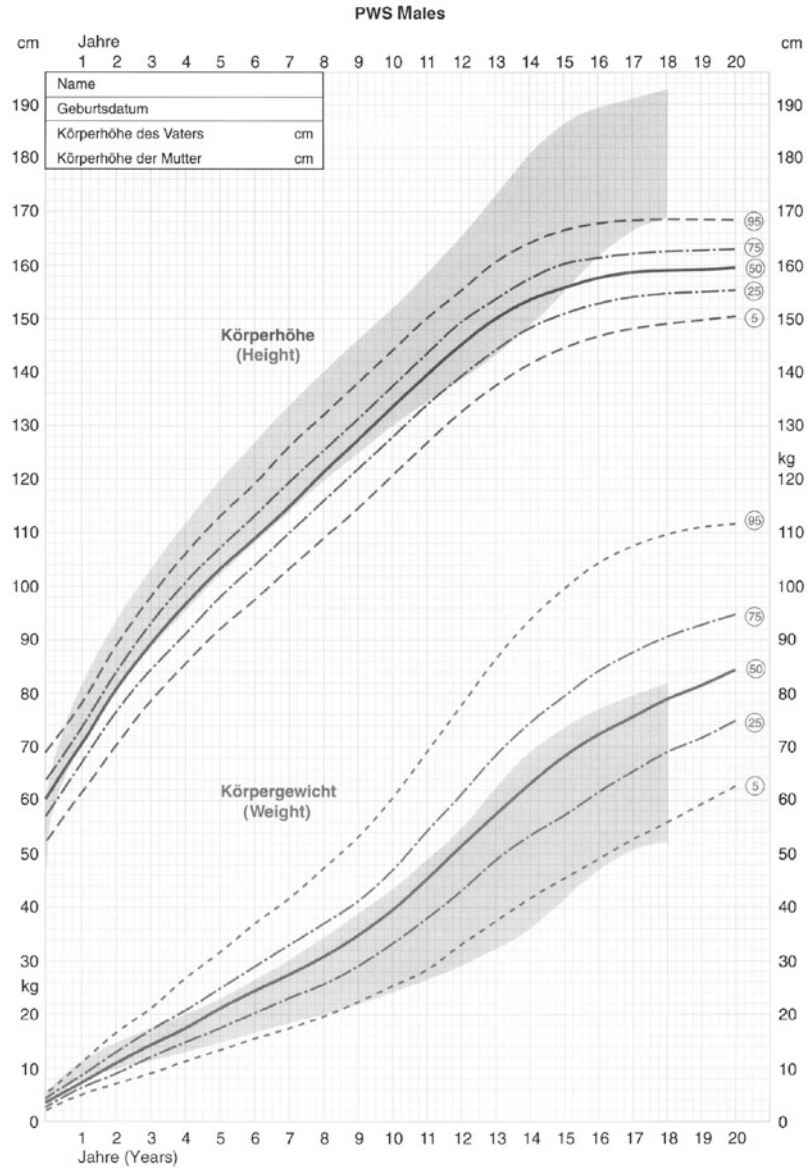

Fig. 26.19 Data from Germany. Centile curves (5th, 25th, 50th, 75th, 95th centile) for length/height (top) and for weight (bottom) of male German PWS patients compared with reference growth standards of normal children (shaded area representing the 3rd to 97th centile range). (Modified clinical chart based on Hauffa et al., *Acta Paediatrica*, 2000, Vol. 89, pp. 1302–1311. Reprinted with permission from Pharmacia Corp. Chart courtesy of Dr. Berthold P. Hauffa)

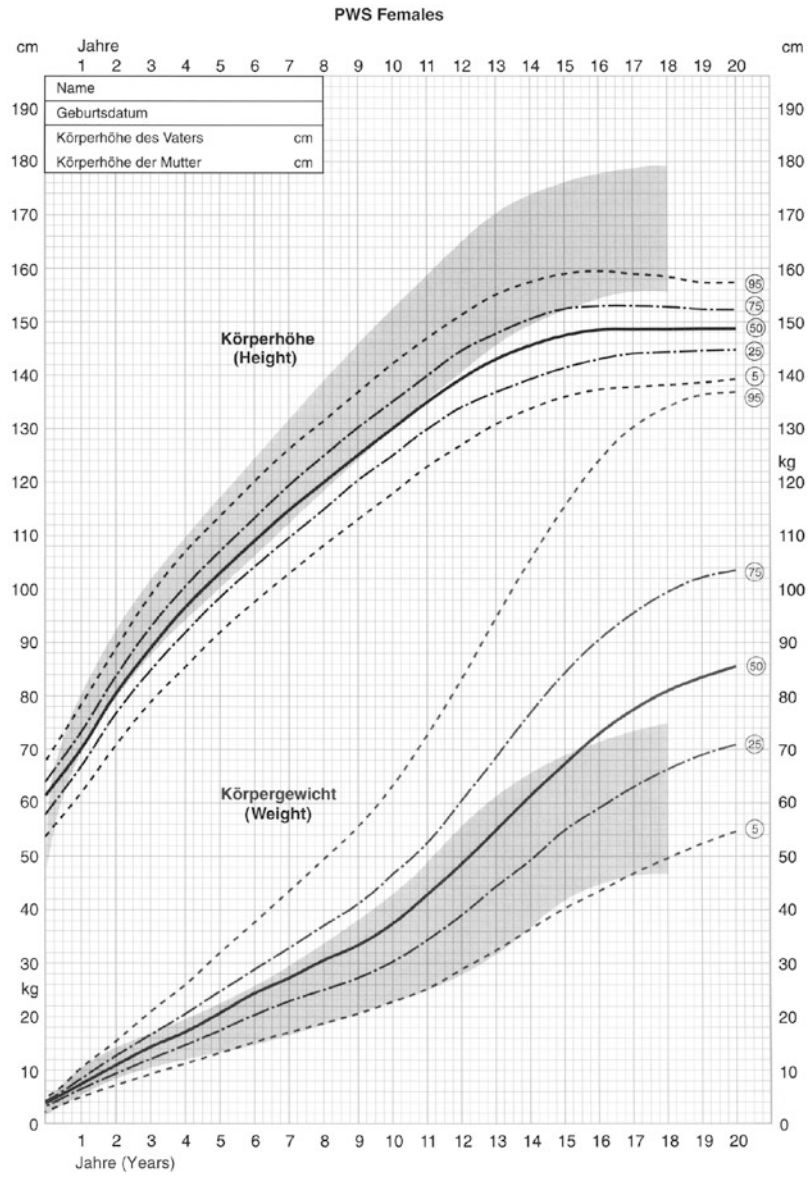

Fig. 26.20 Data from Germany. Centile curves (5th, 25th, 50th, 75th, 95th centile) for length/height (top) and for weight (bottom) of female German PWS patients compared with the reference growth standards of normal children (shaded area representing the 3rd to 97th centile range). (Modified clinical chart based on Hauffa et al., *Acta Paediatrica*, 2000, Vol. 89, pp. 1302–1311. Reprinted with permission from Pharmacia Corp. Chart courtesy of Dr. Berthold P. Hauffa)

Data from Japan

Data in Figs. 26.21, 26.22, 26.23, 26.24, 26.25, 26.26, 26.27, and 26.28 are based on measurements of 252 Japanese individuals with PWS between the ages of 0 and 24 years, including 153 males and 99 females, reported by Nagai et al. The subjects were diagnosed with PWS by clinical, cytogenetic, and/or molecular genetic methods; 198 were found to have a chromosome 15q abnormality (deletion), 26 had maternal uniparental disomy, and in 28 no chromosome analysis was available. Approximately one-third of the subjects were on a calorie-restricted diet. The researchers found that "Growth patterns are not different between Japanese and Caucasian children with the syndrome" but that "the degree of overweight appears much more severe in Caucasians."

Data source: Nagai T, Matsuo N, Kayanuma Y, et al. Standard growth curves for Japanese patients with Prader-Willi syndrome. *Am J Med Genet*. 2000;95:130–4. Original growth charts from this report, courtesy of Dr. Toshiro Nagai, are reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

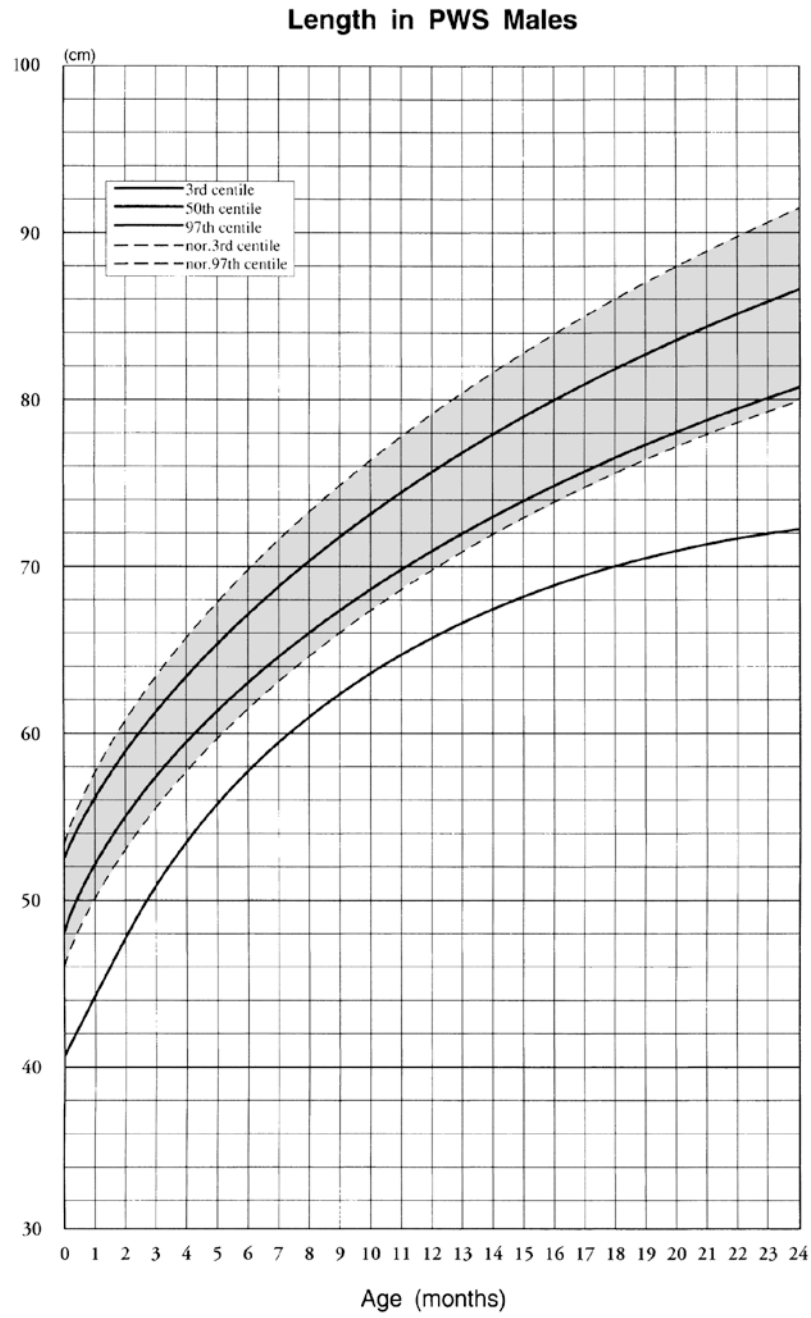

Fig. 26.21 Data from Japan. Body length of male Japanese PWS patients from birth to age 24 months. Solid lines show 3rd, 50th, and 97th centile values for PWS patients and dotted lines show 3rd and 97th centile values for normal children. (From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 131, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai)

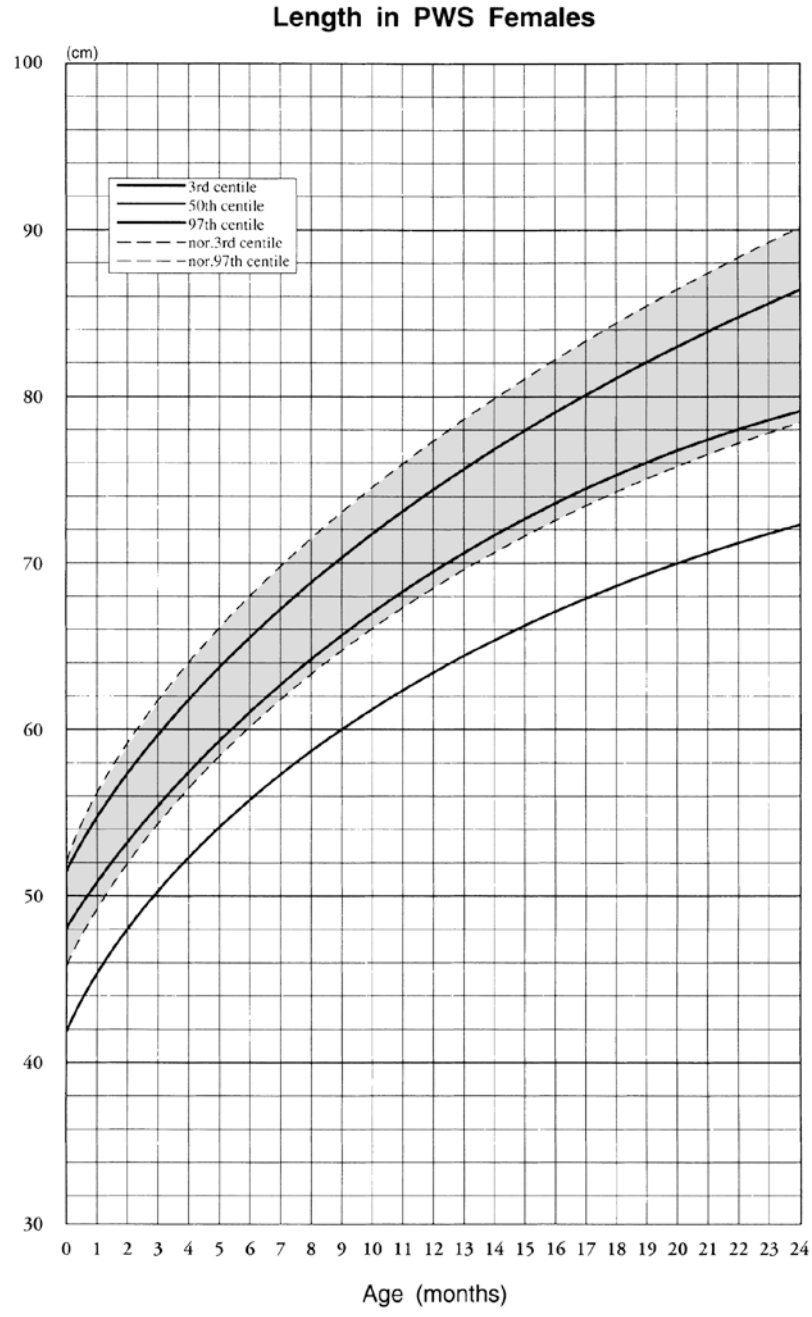

Fig. 26.22 Data from Japan. Body length of female Japanese PWS patients from birth to age 24 months. Solid lines show 3rd, 50th, and 97th centile values for PWS patients and dotted lines show 3rd and 97th centile values for normal children. (From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 131, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai)

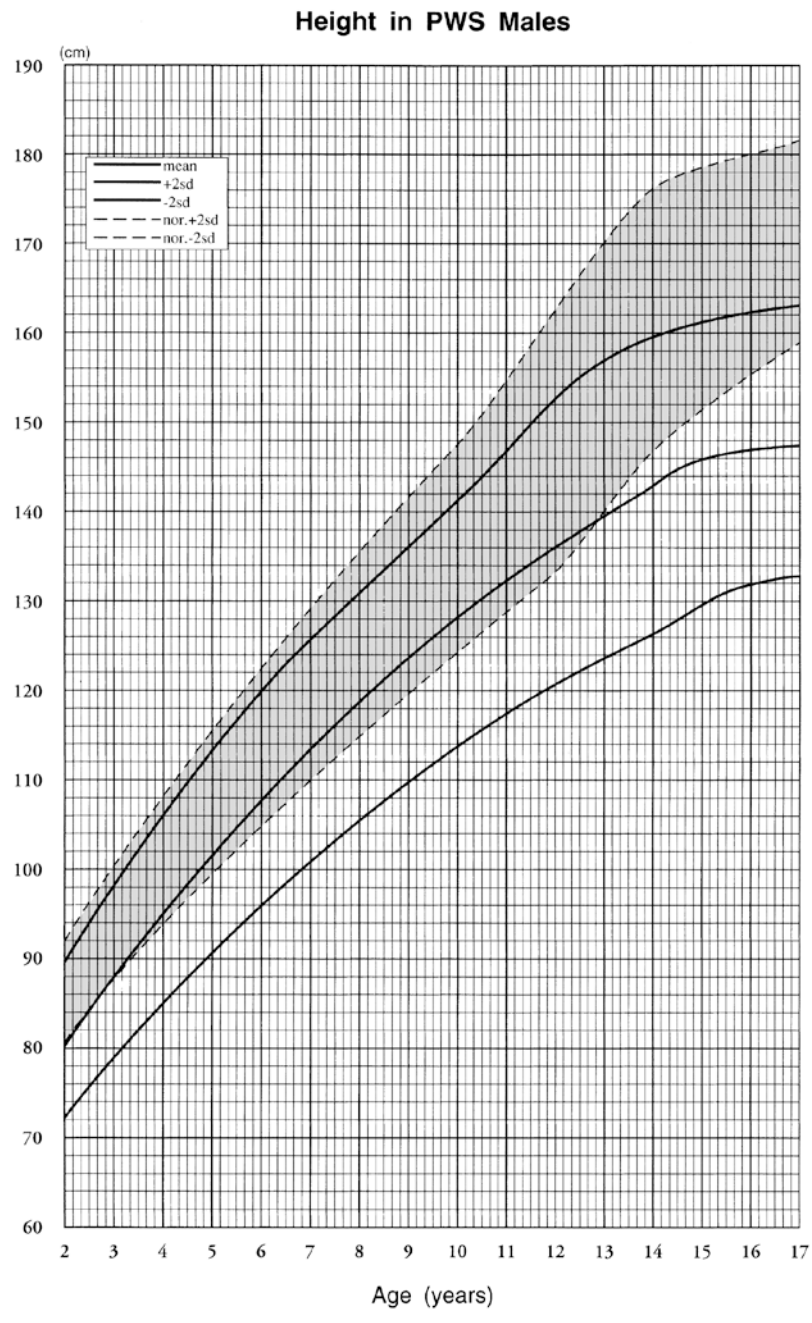

Fig. 26.23 Data from Japan. Height of male Japanese PWS patients from ages 2 to 17 years. Solid lines show 3rd, 50th, and 97th centile values for PWS patients and dotted lines show 3rd and 97th centile values for normal children. (From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 132, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai)

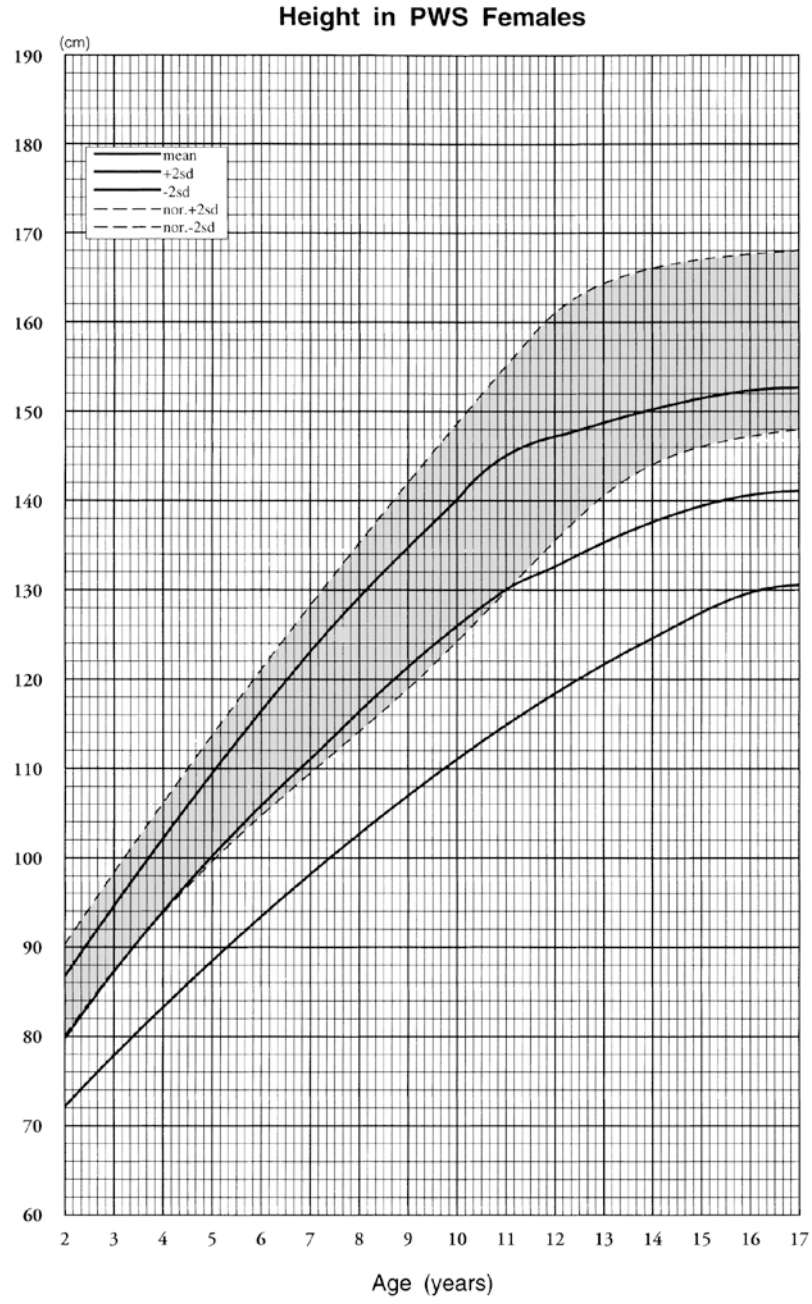

Fig. 26.24 Data from Japan. Height of female Japanese PWS patients from ages 2 to 17 years. Solid lines show 3rd, 50th, and 97th centile values for PWS patients and dotted lines show 3rd and 97th centile values for normal children. (From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 132, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai)

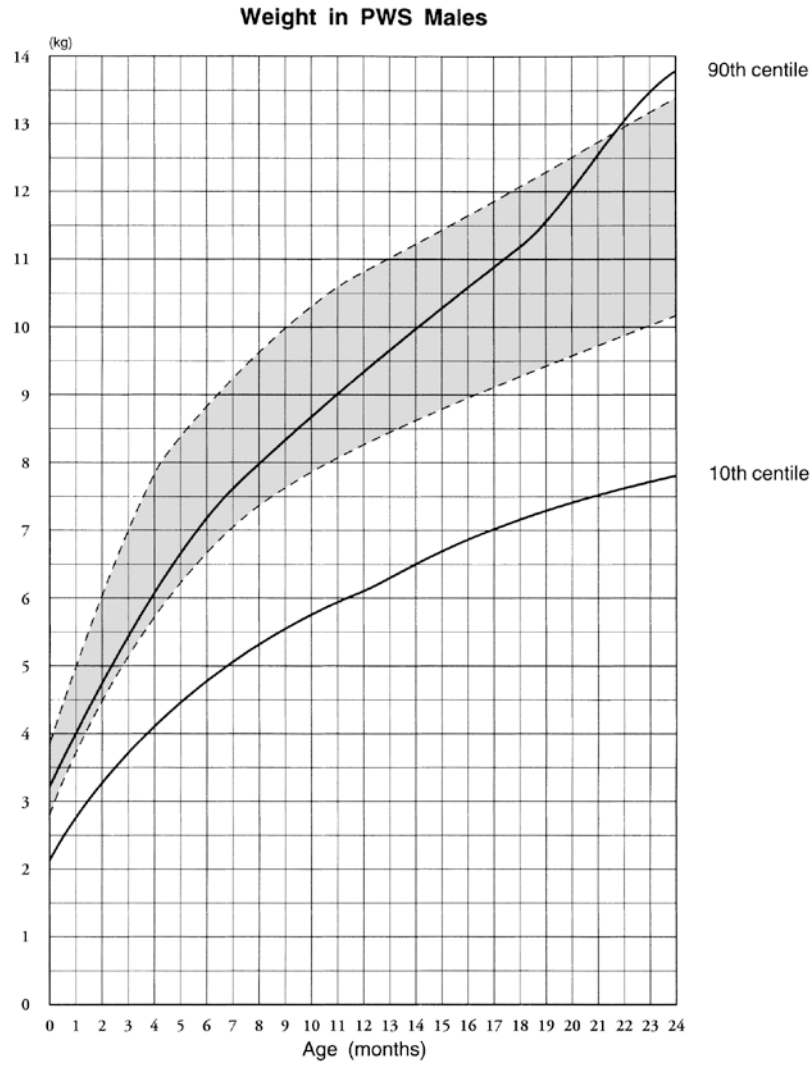

Fig. 26.25 Data from Japan. Body weight of male Japanese PWS patients from birth to age 24 months. Solid lines show 90th and 10th centile values for PWS patients and dotted lines show 3rd and 97th centile values for normal children. (From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 133, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai)

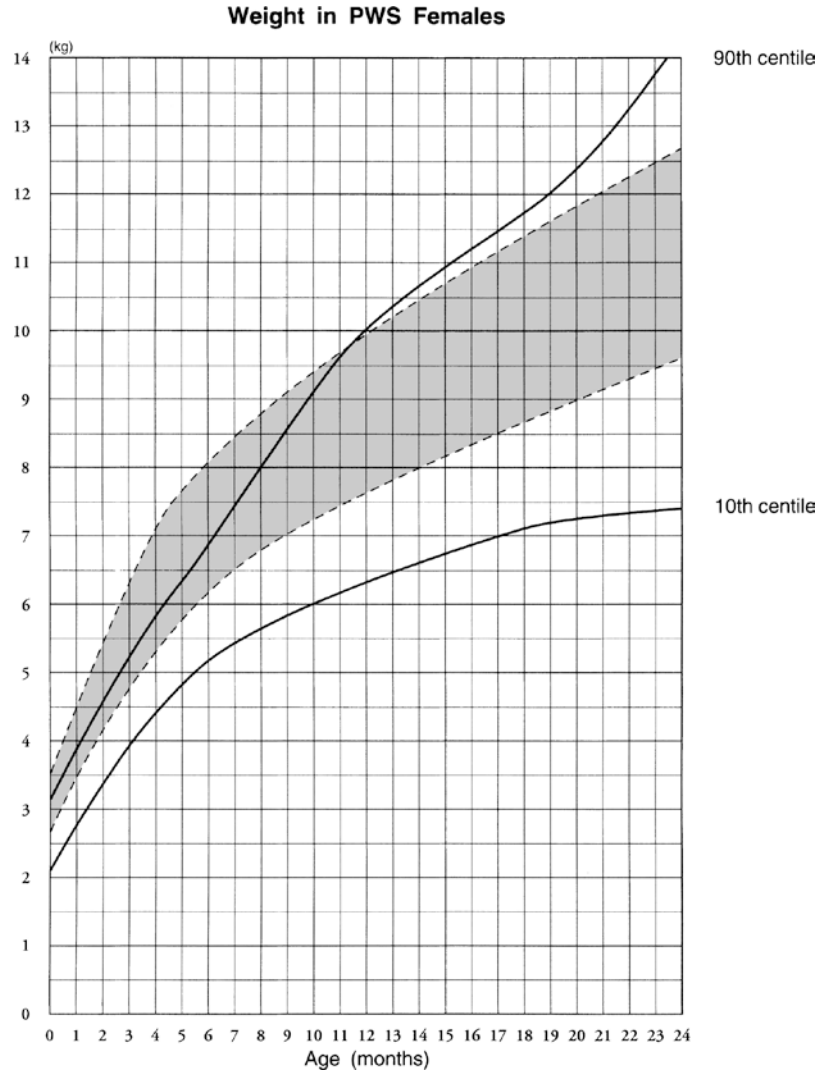

Fig. 26.26 Data from Japan. Body weight of female Japanese PWS patients from birth to age 24 months. Solid lines show 90th and 10th centile values for PWS patients and dotted lines show 3rd and 97th centile values for normal children. (From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 133, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai)

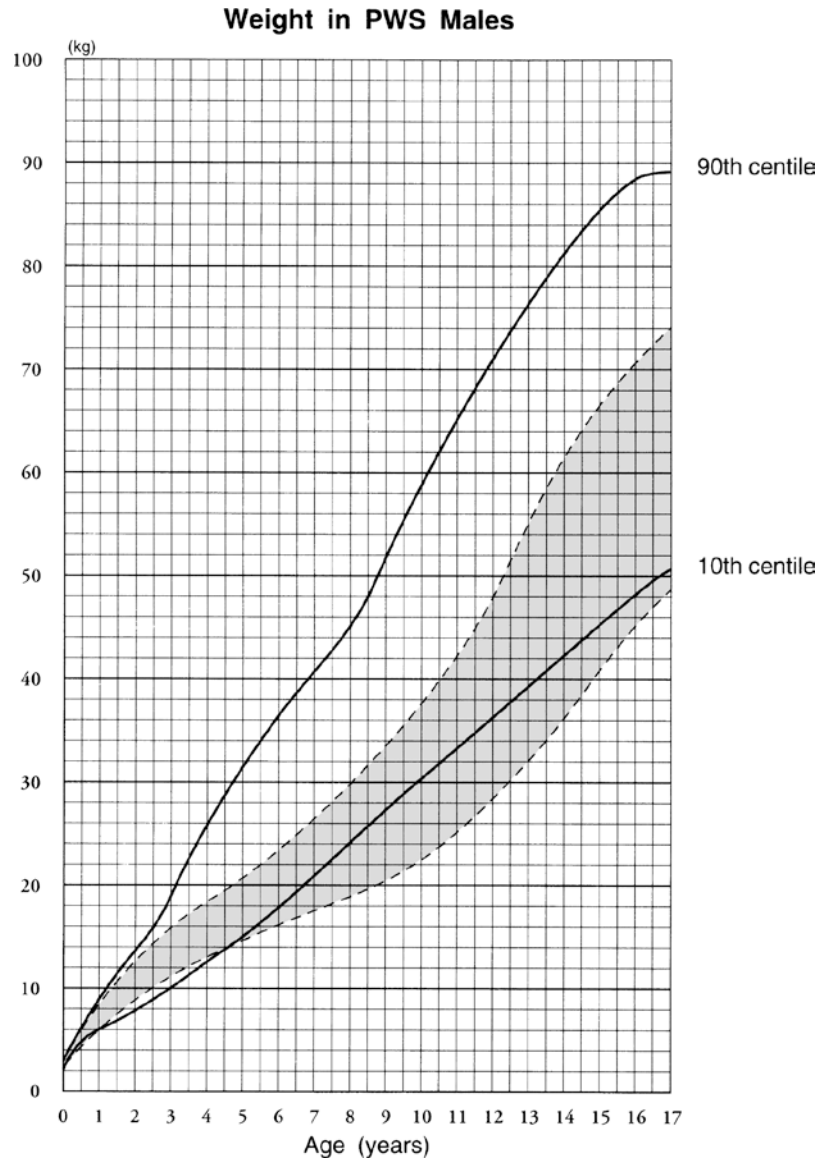

Fig. 26.27 Data from Japan. Body weight of male Japanese PWS patients from ages 2 to 17 years. Solid lines show 90th and 10th centile values for PWS patients and dotted lines show 3rd and 97th centile values for normal children. (From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 133, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai)

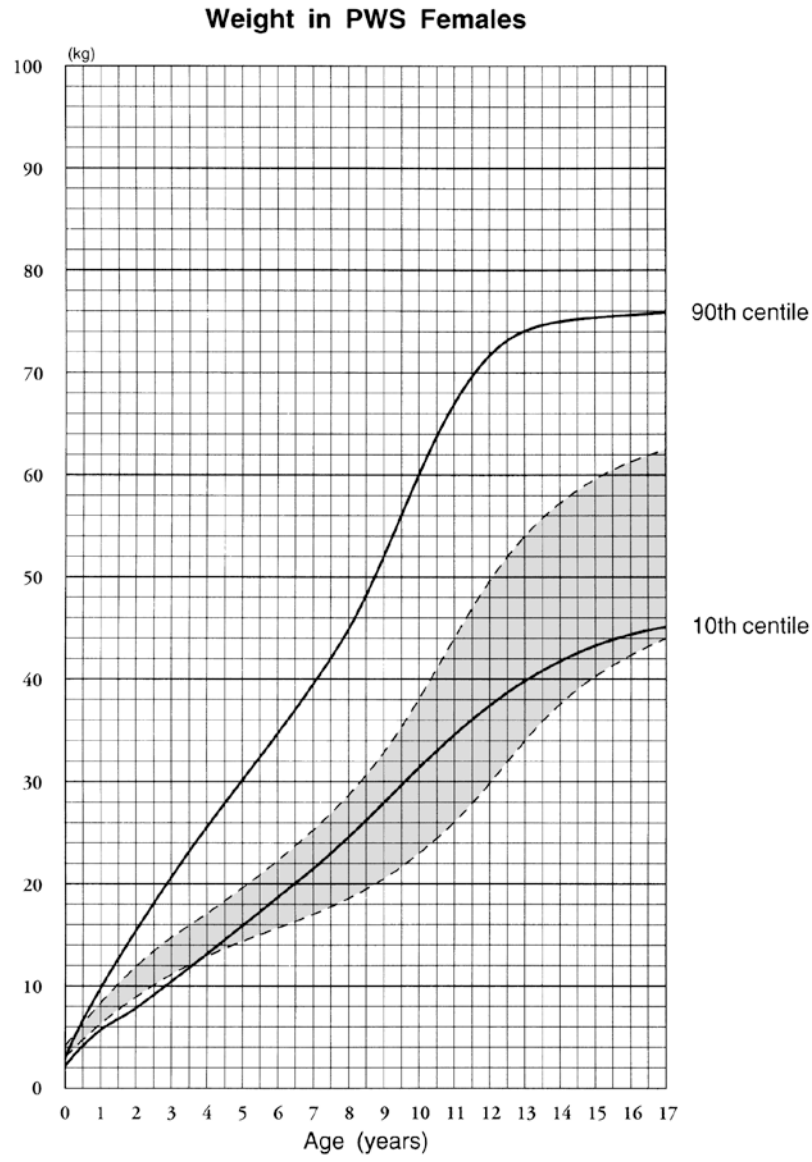

Fig. 26.28 Data from Japan. Body weight of female Japanese PWS patients from ages 2 to 17 years. Solid lines show 90th and 10th centile values for PWS patients and dotted lines show 3rd and 97th centile values for normal children. (From Nagai et al., *American Journal of Medical Genetics*, Vol. 95, p. 133, Copyright © 2000. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Chart courtesy of Dr. Toshiro Nagai)

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