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Prader-Willi Syndrome: Medical Prevention and Behavioral Challenges

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Prader-Willi syndrome (PWS), first described by Prader, Labhart, and Willi in 1956, is a genetic disorder caused by deletion or impaired expression of paternal genes in a critical area of chromosome 15. The incidence ranges from 1:10,000 to 1:20,000 births, with equal distribution in both sexes and all ethnic groups [1]. This neurogenetic multisystemic disorder is characterized by infantile hypotonia, mental retardation, feeding difficulty in infancy that evolves to an extreme drive to eat in childhood, dysmorphic features, short stature, hypogonadism, sleep apnea, diabetes, and severe maladaptive behaviors, including obsessive, compulsive, and oppositional behaviors. There is a widely accepted view that the neurologic underpinnings of PWS involve hypothalamic dysregulation; however, brain imaging techniques suggest that other brain regions are also involved [2,3].

We begin this article with a brief discussion of the genetic basis of PWS followed by a description of the characteristic medical features, the comorbidity associated with this syndrome, a review of endocrine abnormalities, and hormonal treatment. We present the profile of intellectual impairment and the characteristic pattern of maladaptive behavior, with emphasis on the psychiatric aspects of PWS, and conclude with a discussion of behavioral and institutional treatment issues.

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Genetics

Deletion or abnormal expression of paternal genes in chromosome 15q11-13 can result in the Prader-Willi phenotype. Complete or partial deletion of paternal 15q11-q13 accounts for 70% of affected patients, whereas approximately 25% have uniparental maternal disomy (UPD). In normal chromosome pairs, each chromosome is derived from a different parent. The term ''uniparental disomy'' indicates that both copies of a particular chromosome derive from only one of the parents. Inheriting both copies of chromosome 15 from the mother results in PWS. Older maternal age seems to be a more common factor in patients who have UPD and is associated with meiotic nondisjunctive events that result in uniparental disomic zygotes [4,5]. An estimated 1% to 5% of patients who have PWS have a mutation in the imprinting center, which causes abnormal gene expression despite the presence of anatomically intact paternal and maternal chromosomes 15 [4–6]. Imprinting refers to the differential expression of genetic material depending on whether the gene is derived from the mother or father. If a gene is paternally imprinted, the gene derived from the father is inactive and only the gene derived from the mother is expressed. Microdeletions, detected by sequence analysis, have been reported in only 15% of patients with proven imprinting defects.

The inheritance of PWS is almost always sporadic. The risk to siblings and other first-degree relatives is less than 1% when the molecular defect is a deletion or UPD. A mutation in the imprinting center, found in 1% to 5% of patients, carries a 50% risk of family recurrence. Determination of the specific type of genetic defect is essential for counseling parents regarding risk to future offspring.

Fluorescent in situ hybridization detects nearly all patients with deletions in the 15q11-q13 region. A technique using microsatellite markers can determine if all of the alleles are of maternal origin (UPD). The most sensitive method for detecting nearly all cases of PWS, however, is DNA methylation analysis. The diagnosis of PWS is confirmed by finding a methylation pattern characteristic of exclusively maternal alleles. Patients who are suspected of having PWS should first undergo methylation analysis. If the methylation test result is positive, fluorescent in situ hybridization or microsatellite studies can be applied subsequently to determine the exact type of molecular defect present.

Although PWS is not included in routine prenatal screening, the severity of this syndrome may justify inclusion of PWS in routine prenatal genetic disease screening.

Medical considerations

Medical problems are inherent within the clinical diagnostic criteria of PWS and differ according to the stage of life [7]. Perinatally, the manifestations are difficult delivery, central hypotonia, poor sucking, motor delay, and failure

to thrive, which often necessitate special feeding techniques such as nasogastric tubes. The characteristic dysmorphic features include dolichocephaly and almond-shaped eyes. Small mouth, hands, and feet, speech articulation defects, and a distinct prosody become apparent in childhood. In adulthood, mild hypotonia with decreased muscle bulk and tone is present [8].

The resting metabolic rate is lower than expected for age. This rate, in combination with a low level of general motor activity and overeating, leads quickly to severe morbid obesity. The obesity is central in distribution and is the major cause of morbidity and mortality: cardiopulmonary compromise, type 2 diabetes mellitus, hypertension, thrombophlebitis, leg edema, and sleep apnea [8]. The abnormal metabolic rate may account for the prolonged and exaggerated responses to standard dosages of medications and anesthetic agents [9,10].

Sleep and breathing disorders are attributed to central dysfunction although exacerbated by obesity. The manifestations of nocturnal breathing abnormalities are excessive daytime sleepiness, abnormal ventilatory responses to hypoxia, and hypercapnia. Treatment includes adenotonsillectomy, nocturnal ventilation, weight control, and behavioral interventions [11]. Orthopedic problems, such as scoliosis/kyphosis and osteoporosis, are frequent [7].

Thick, viscous saliva may predispose to dental caries and contribute to articulation problems and can complicate airway management. Products for increasing saliva production have proved beneficial in treating dry mouth and improving dental hygiene [8].

High pain threshold, decreased vomiting, and altered homeostatic hypothalamic control of body temperature characterize PWS. As a result, subtle signs or symptoms can be the harbinger of serious underlying disease. Physicians should be alert to changes in behavior, temperature, mood, or minor complaints in individuals who have PWS [12]. In light of hyperphagia and possible ingestion of spoiled food, lack of or the presence of vomiting may signal a life-threatening illness. Controversy exists as to whether sudden, unexpected death is a feature of PWS and if the life expectancy is decreased compared with the general population [13].

In conclusion, the medical picture of individuals who have PWS involves multiple systems: central nervous, respiratory, gastrointestinal, cardiovascular, dermatologic, and urogenital. Medical treatment demands prevention and treatment of weight gain because most of the serious medical problems are a direct consequence of morbid obesity. A multidisciplinary approach with anticipatory care and appropriate attention to medical problems as they occur can improve the quality of life of patients who have PWS.

Endocrine disorders and hormonal treatment

Children who have PWS show variable degrees of impaired growth hormone (GH) secretion along with low levels of serum insulin and insulin-like growth factors. If untreated, 50% of individuals who have PWS

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fail to reach a normal adult height. GH treatment of these children results in a significant and persistent increase in height velocity and height standard deviation scores [14].

Beyond increasing final height, GH has other important beneficial effects in patients who have PWS. Infants in whom GH treatment was started before age 18 months show significantly increased mobility skill acquisition. In children who were treated before 3 years, there is decreased percent body fat mass and increased lean body mass. Older children and adolescents maintain a sustained decrease in body fat mass and increased lean body mass and bone mineral density [15]. Resting energy expenditure is also increased [15]. Pulmonary function, measured by peak flow rate, vital capacity, and forced expiratory flow, improved during 6 months of GH treatment [16].

Although side effects of GH treatment in children are rare, there are concerns that children who have PWS may be at increased risk for worsening of scoliosis, development of diabetes mellitus, and death from obstructive sleep apnea or central hypoventilation. Among 328 children who have PWS who were treated with GH for 1 to 2 years, 5 developed type 2 diabetes mellitus and one case of type 1 diabetes was observed [17]. Monitoring for scoliosis is recommended during treatment because scoliosis is common in PWS and may worsen as linear growth increases.

Reports of sudden death in children who have PWS receiving GH raised concerns of increased mortality in these patients. To date, however, there is no convincing evidence that children treated with GH have a higher mortality rate than nontreated patients [17,18]. Although GH may stimulate growth of lymphoid tissue, including tonsils and adenoids, and exacerbate any pre-existing obstructive sleep apnea, GH exerts beneficial effects on respiratory function by decreasing body fat mass while increasing lean body mass. Additional risk factors for mortality include severe obesity and concurrent upper respiratory tract infections. A strict dietary and behavioral program of weight control should be initiated before starting GH treatment, and a sleep study should be conducted to evaluate oxygen saturations or sleep apnea. We also recommend repeating the sleep study 1 month after onset of treatment. If there is an increase in sleep apnea or hypoxia, GH treatment may need to be stopped until the factors contributing to impaired respiratory function are corrected. It may be prudent to withdraw GH treatment during acute upper respiratory or other intercurrent infections.

Hypogonadism is a consistent feature of PWS; cryptorchidism and micropenis are common—although not universal—findings. Boys undergo some pubertal development, but midpubertal arrest generally occurs. Most girls undergo spontaneous development of breast tissue during adolescence, probably because of estrogen production from peripheral aromatization in adipose tissue. Spontaneous menarche has been described in 44% of girls older than age 15 years, but menses are often limited to periodic spotting [19]. Pregnancy was reported in two women with genetically documented PWS. Fertility has not been reported in men who have PWS.

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It has generally been assumed that hypogonadism in PWS is explained by gonadotropin deficiency caused by hypothalamic dysfunction. Recently, Eiholzer and colleagues [20] found that boys who have PWS may have a combined central and peripheral hypogonadism that consists of low leutinizing hormone levels along with low inhibin B and high follicle-stimulating hormone levels. These findings suggest that boys who have PWS have a primary Sertoli and/or germ cell defect or early germ cell loss.

The medical rationale for sex hormone replacement therapy includes prevention or treatment of osteoporosis, improvement of muscle mass and function by androgen replacement in male patients, and prevention of the albeit rare possibility of pregnancy by use of oral contraceptives. Testosterone may be administered as an intramuscular depot preparation (testosterone enanthate in oil) at intervals of 2 to 4 weeks, starting with a low dose of 50 mg every 4 weeks and gradually increasing to full adult replacement of 200 mg every 2 weeks. Peak and trough testosterone levels on the intramuscular regimen may result in aggressive behavior and emotional lability. Testosterone patches may be preferable because they provide stabile levels of testosterone. Oral contraceptives that contain a low dose of estrogen are usually adequate to maintain regular menses and prevent deterioration in bone density. In addition to sex hormone replacement, calcium and vitamin supplements should be recommended when low bone density is found.

Cognition

Mental retardation is a major characteristic of PWS. In a meta-analysis of 575 people who have PWS, only 5% were of normal intelligence, one third were found to be moderately retarded, and most were in the borderline mildly retarded range. No IQ decline was seen with age [21]. Unfortunately, their immature social behavior often masks their intellectual abilities [22].

A pattern of cognitive strengths and weaknesses is apparent, although not all individuals who have PWS show this profile [21]. As a group, their main strengths are in the domains of visuospatial performance, reading and decoding, long-term memory, and exceptional skills with jigsaw puzzles [23,24]. Areas of disability are short-term memory, auditory processing, socialization, and mathematical skills. They also show low performance in sequential as opposed to simultaneous processing [23].

Individuals who have the UPD genetic type may display slightly higher cognitive skills than individuals with deletions. The differences reported are that individuals who have UPD have a higher average verbal intelligence and impaired coding ability. One hypothesis is that these differences are a manifestation of the influences of gender-specific imprinted genes on cerebral lateralization, a hypothesis that needs further investigation [25].

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To date no comprehensive study has assessed executive functions in children who have PWS. Even attention deficit hyperactivity disorder, in which executive functions are typically impaired, only recently has been documented in PWS [26,27]. The severe medical problems may divert attention from the impaired executive functions and attention deficit hyperactivity disorder. In persons with relatively high IQ, impaired executive functions may be a partial explanation for the apparent discrepancy between their intelligence and their overall low level of academic, neuropsychological, and social functioning [26].

In a pilot study on adults who have PWS, beneficial effects in mental speed, flexibility, and motor performance during GH treatment have been reported [28]. It is essential to recognize and address the specific cognitive characteristics of persons who have PWS and their areas of strength and disabilities, which will enable therapists to tailor educational interventions to achieve optimal expression of intellectual abilities.

Behavioral characteristics and psychiatric issues in Prader-Willi syndrome

Behavioral patterns are remarkably consistent among persons who have PWS, albeit with a wide spectrum of intensity and frequency. The characteristic symptom complex is often termed ''the behavioral phenotype of PWS,'' which qualifies persons who have PWS for an Axis I diagnosis of ''personality change due to a medical condition'' [29]. Forster and Gourash [30] suggested a useful classification in domains that we have modified in accordance with our clinical experience.

Food-seeking related behaviors

The endless pursuit for food starts around the age of 6 years. The core abnormality is not an increased appetite but an impaired satiety response [31]. If unrestricted, persons who have PWS can eat enormous quantities of food, and when regular food is unavailable, they eat frozen, raw, or even pet food. One of our patients left his sheltered group house for 13 hours without any supervision and gained 29 pounds during that short period. Common techniques for obtaining food are night raids to the kitchen, manipulating well-meaning adults, and taking food from the garbage or other children's bags, but may also include begging, lying, stealing, and breaking locks. The pursuit for food may culminate in dangerous behaviors, such as providing sex services in exchange for food. To date, there is no effective medication to ameliorate this problem [32]; its management requires 24-hour-a-day supervision, restrictive measures, planned physical activity, and a strict diet ($\leq$1200 cal/d) divided into consistently scheduled meals. Every person in the immediate environ must be cognizant of the deleterious effect food has for the person who has PWS.

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Traits indicating lack of flexibility

Children who have PWS sometimes can be described as stubborn, insisting on sameness, and unable to adjust to changes already at the age of 5 years. They tend to get stuck on certain issues, perseverating in their speech or repeatedly asking the same question. They need a predictable and unchanging daily schedule, because slight deviations from the usual routine can result in severe temper tantrums. This reaction may be caused, at least in part, by impaired executive functions and low performance in sequential processing (see the section on cognition), which render them dependent on learned routines and acquired patterns.

A second aspect of the inflexibility in individuals who have PWS is the development of rituals, which range from simply collecting useless items or hair pulling to bizarre rituals, such as playing with feces. Compulsive behaviors, examples of which are skin picking, hoarding, ordering, and ''just right'' phenomena, are more frequent in patients who have PWS than among patients who have other developmental disorders, with the exception of pervasive developmental disorder [33,34]. Skin picking is seen in at least one third of the patients and may cause severe skin infections. Anal and vaginal digging are more common than reported by patients, and the resulting bleeding can lead to unnecessary medical investigations [35,36]. Although the exact prevalence of full-blown obsessive-compulsive disorder in PWS is unknown, symptoms cause significant impairment in more than 45% of individuals who have PWS [33].

Oppositional behaviors and interpersonal problems

Children who have PWS challenge the caregivers' consistency and will for maintaining limits, not only in food-related issues. These children are egocentric and argue, lie, manipulate, and confabulate to change rules, obtain their wishes, or justify misbehavior. Their social judgment is poor, even considering their intellectual ability, and interpretation of visually presented social information is on a level with that of children who have pervasive developmental disorder [37]. When these interpersonal disabilities are compounded to the repetitive behaviors in PWS, overlapping many seen in pervasive developmental disorder [33], it is not surprising that the prevalence of pervasive developmental disorder among persons who have PWS is high [38].

Traits indicating abnormal emotional regulation

Children who have PWS have little tolerance for uncertainty, to which they respond with explosive behavior, and they react to minor frustrations with temper tantrums. Their affective regulation is also disturbed, manifested by mood swings from joy to irritability. The impaired satiety response, skin picking, and high pain threshold also can be viewed as the

consequence of impaired regulatory mechanisms. Gourash and Forster [39] have suggested that these traits may represent a failure in modifying feedback pathways.

Several studies have found that most maladaptive behaviors, including self-injury, stealing, and obsessive-compulsive symptoms, are significantly more severe in persons who have PWS whose genetic defect is deletion (compared to individuals who have UPD) [40,41]. IQ, family environment, and parenting styles also impact on the behavioral traits, however, and result in a great variability among individuals who have PWS. It is essential to have an accurate record of the behavioral baseline of each patient at each developmental stage, including frequency and intensity of each symptom, for at least two important reasons:

- In persons who have PWS, the main reaction to any stressor is exacerbation of these symptoms. Changes in the behavioral baseline can be the first cue to uncover a psychological cause of distress (eg, secret abuse, traumatic stress) or a physical illness.
- Accurate monitoring of these symptoms is essential for a differential diagnosis between the characteristic behavioral profile and the comorbid psychiatric disorders in individuals who have PWS.

Comorbid psychiatric disorders

Levels of psychopathology are found to be higher among persons who have PWS than among persons with intellectual disability of other origins [42]. Attention deficit hyperactivity disorder and obsessive-compulsive disorder already have been discussed, and this section focuses on mood and psychotic disorders.

Sudden bursts of disturbed mood, as part of the "normal" behavioral pattern in PWS, are generally trigger-dependent and short lived. During adolescence, prolonged waves of restlessness and dysphoric or anxious mood may appear. Preoccupations that cause severe distress tend to dominate the thought content but either resolve spontaneously within a few days or evolve into clinical depression. In some cases there is a rapid change into a hypomanic episode, with confusion, restlessness, and increased goal-directed behavior that lasts a few days to a few weeks. In 15% to 17% of persons who have PWS, these two latter clinical developments are sufficiently prolonged and profound to justify a diagnosis of mood disorder [43].

During late adolescence and adulthood, delusions, most often of paranoid type, may appear in the course of one of these waves of disturbed mood. Hallucinations are not common in individuals who have PWS. This high risk for psychotic episodes is almost exclusively associated with the UPD or imprinting genetic types [44]. The combination of cyclic mood disturbance and delusions is consistent with the European diagnostic

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category of ''cycloid psychosis,'' which is frequently used in publications on PWS. Boer and colleagues [44] reported a prevalence of 28% for severe affective disorders with psychotic features in this age group.

Psychopharmacology

The therapeutic and side effects of medications in patients who have PWS often can be greater than expected, even in severely obese patients who receive low dosages when considering their body weight. For many patients, one fourth to one half of the normally prescribed dose is sufficient, whereas usual dosage levels may cause toxic reactions or exacerbation of behavior problems [9]. Severely reduced metabolism by some components of cytochrome 450, a metabolic abnormality documented in one third of individuals who have PWS, may partly explain this sensitivity to medications [10].

There is no specific pharmacologic treatment for the behavioral disturbances typical of PWS. No safe drug has been found to be effective against hyperphagia. The only candidate found to justify a controlled study was fenfluramine [45]. Although the trial was successful, this medication is currently considered unsafe because of cardiopulmonary adverse effects. Anecdotal reports and a few open-label trials suggested the effectiveness of some symptomatic psychopharmacologic interventions [32]. Selective serotonin reuptake inhibitor drugs may result in some improvement in compulsions, anxiety, and mood, although they may trigger severe mood switches and require careful monitoring of mood response. Carbamazepine has reduced violent outbursts in two case reports [32]. Recently, two open-label studies (12 patients in total) showed positive effects of topiramate on mood and skin picking [35,36]. From our experience, methylphenidate is effective in treating symptoms of attention deficit hyperactivity disorder in PWS but does not decrease appetite. Atypical antipsychotic drugs in low doses can be helpful during psychotic episodes. It is important to keep in mind that some of these episodes are reactive to an environmental stress, such as grief, so in these cases it is justified to consider withdrawal of medications [30]. Neuroleptics can be used when behavior and emotional control become dangerously impaired despite satisfactory environmental treatment. Low doses of risperidone in seven patients resulted in notable improvement in maladaptive behaviors during a 37-week follow-up, and patients did not experience weight gain [46].

In periods of severely disturbed behavior, a wise combination of psychiatric medication and behavioral measures seems to be the best option. Professionals who treat persons who have PWS are sometimes challenged by such severe and continued behavioral disruptions that they may be tempted to consider medications or psychiatric hospitalizations as ''quick fixes'' for these individuals. It is essential to keep in mind that most

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maladaptive behaviors are part of the basic phenotype of PWS, which needs sustained efforts to find effective behavioral strategies, generally the only way to improve adaptation in the long-term.

Behavioral and institutional treatment

Managing behaviors of people who have PWS can be successful in the long-term if a comprehensive and consistent approach is implemented [9,47]. The treatment should focus on food- and non–food-related behaviors. As for the food-related issues, the most basic aspect of any program is having all food under lock and key and granting no access without parental or staff supervision. It is critical that all food-related activities be structured and consistent, including meal times, the particular diet and foods served, portioning, and availability of second helpings. Any changes from these routines often result in tantrums, stealing, and other negative behaviors. Firm and consistent rules and limits enable persons who have PWS to behave at their best.

When regulatory issues concerning food are completely out of the control of the person who has PWS, behavior management of other issues becomes possible. Persons who have PWS function best when their daily schedule is composed of preplanned activities consistently implemented, which allows them to plan based on the knowledge of what to expect in any given hour of any given day [9]. Visual cueing allows for better communication, because their auditory skills are inferior to visual processing. The following techniques are among the behavioral techniques commonly in use [47]:

- Token economies (point systems) may help children and adolescents who have PWS by concretizing the behavioral demands and giving an incentive to comply. Points are earned for accomplishment of specific tasks or goals, such as physical exercise or maintaining diet. Positive feedback should be given after desired behaviors and undesirable behaviors, if possible, should be ignored.
- Relaxation exercises can be used to release tension.
- Persons who have PWS can be taught to restructure their cognitions in ways that promote better emotional states and behaviors in accordance with the cognitive model that stimuli are processed first cognitively and then emotionally, and finally the behavioral response appears.
- Teaching basic problem-solving skills, which are rehearsed in role playing, results in a wider and healthier repertoire of behavioral responses.

One of the teaching methods is "video group behavioral therapy," in which there is role playing of problematic situations from real life. The role playing is repeated until there is a better behavioral outcome. They are able to watch and listen to themselves on TV, with the goal being to maximize learning [48].

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Local PWS associations have an important role as a framework for support and self-help. They also provide important information in the local language for families, physicians, and teachers.

The severity of maladaptive behaviors and the need for continuous supervision and restrictive measures leads frequently to the conclusion that residential treatment is a necessity [9,47]. Several different sheltered living programs exist, some of which are exclusively for people who have PWS and others that include a mixed population. There are group homes or apartments in which each resident has an apartment or room in a complex of sheltered apartments. There are also large institutions in which one of the facilities is for people who have PWS and the other houses are for individuals who have other disorders.

Different solutions have evolved in various countries. In the United States, small community-based group homes are the most common residential program. In Scandinavia, the apartment model became the most common solution for sheltered housing in homogeneous and heterogeneous populations. In Israel, the only residential program is a large group home exclusively for people who have PWS, which is divided into two separate buildings located in a residential suburb of Jerusalem. The main building has a locked central kitchen, individual bedrooms, a small exercise room, a living/dining room, staff offices, and an enclosed yard. The other house has locked food storage, bedrooms, bathrooms, living/dining area, and additional communal space.

There is a great deal of controversy regarding the relative merits and disadvantages of homogeneous versus heterogeneous populations when dealing with PWS. Among the negative issues to be considered are the food limits imposed on residents who do not have PWS and consternation of residents who do have PWS when confronted with eating habits of residents who do not. Because some group activities require adequate motor skills not available to the population who has PWS, they might find themselves too often in the role of spectators. In a more positive vein, there are opportunities for enhanced socialization in a heterogeneous population, although their lack of sexual development and need for supervision often limits their desirability as partners for more independent social activities and outings. It would be interesting to use quality-of-life measures to determine which of the options available provides solutions most congenial to the population who has PWS.

The multidisciplinary approach

The complexity of the clinical problems in patients who have PWS requires an approach that integrates the different professional fields involved. The PWS multidisciplinary clinic at our institution is one model of integrated care. The clinic staff includes specialists in pediatric neurology, child psychiatry, endocrinology, psychology, orthopedics, and nutrition during a single clinic visit. Consultations with pulmonary and ear, nose, and throat

physicians who are familiar with PWS are obtained as needed. Patients from all parts of the country are seen in our clinic at least once a year for a routine follow-up or at times of crisis, when the therapists in charge of the daily management in the community request additional assistance.

Epilogue

Preventing morbid obesity and managing the maladaptive behaviors in persons who have PWS are the most important goals that require lifelong commitment of the therapists. When the person is an adult and capable of making informed decisions, restrictive supervision raises serious legal and ethical dilemmas that demand balance among quality of life, life-saving cohesive measures, and free will [49]. Food is not the only treatment issue that needs confrontation; sexual behaviors, diabetes mellitus, scoliosis, and devices for the treatment of nocturnal respiratory disorders are additional therapeutic fronts that need consent and compliance from the maturing individual who has PWS. Although these issues are beyond the scope of this article, they highlight the treatment dilemmas involved in managing this multisystemic disorder that only becomes more complex with increasing age. We can only emphasize the need to approach each person who has PWS as an individual, be sensitive to traits and strengths (related to and especially unrelated to PWS), and choose among the therapeutic approaches most appropriate.

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