Prader-Willi syndrome

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Abstract

Prader-Willi syndrome (PWS) was first described in 1956 in Zurich by Prader (1956). They pictured a syndrome characterized by small stature, obesity, hypogonadism, cryptorchidism, and oligophrenia with a history of extreme muscular hypotonia in the neonatal period. PWS is seen as a complex, multisystem disorder and is the most common genetic cause of marked obesity. Estimates of the incidence range between 1:10,000 and 1:30,000. PWS occurs in all ethnic groups.

Keywords

Behavioral problems; Cognitive disability; Developmental delay; Growth hormone; Hyperphagia

Glossary

Hypogonadism Decreased or nonexistent hormone secretion by the gonads. The gonads refer to both sex glands, the female ovaries and the male testes.

Hypothalamic dysfunction Abnormal function of the region of the brain called the hypothalamus. The hypothalamus helps to control the pituitary gland. The pituitary gland in turn controls the thyroid gland, the adrenal glands, ovaries and testes. The hypothalamus also helps to regulate energy balance, body temperature, salt and water balance, emotions and is involved in growth, milk production, childbirth, and sleep.

Hypotonia Reduced muscle tone, present in every newborn with PWS. There is a feeling of floppiness when the baby is held.

Obesity Excess body weight, defined as a body mass index greater than 30 kg/m^2 in adults or, greater than the 97th percentile of normal reference values in children.

Key points

- Prader-Willi syndrome (PWS) is a complex neurogenetic disorder and the most common genetic cause of obesity. It is associated with growth hormone deficiency, hypogonadism, hypothalamic dysfunction, obesity, short stature, mental retardation, and developmental delay.
- Growth and sex hormone therapy plays a critical role in the treatment of PWS, improving height, body composition and metabolic outcomes.
- Hyperphagia and reduced physical activity as well as behavioral problems require multidisciplinary intervention.
- Comprehensive care includes strict caloric restriction, growth and sex hormone treatment, daily exercise, and family coaching.

Introduction

Prader-Willi syndrome (PWS) was first described in 1956 in Zurich by Andrea Prader, Alexis Labhart, and Heinrich Willi (Prader (1956). They pictured a syndrome characterized by small stature, obesity, hypogonadism, cryptorchidism, and oligophrenia with a history of extreme muscular hypotonia in the neonatal period (Fig. 1). PWS is seen as a complex, multisystem disorder and is the most common genetic cause of marked obesity. Estimates of the incidence range between 1:10,000 and 1:30,000. PWS occurs in all ethnic groups.

The syndrome is caused by an absence of the expression of the paternally active genes in the PWS critical region on chromosome region 15q11.2–q13. In 65–75% of individuals, this occurs as the result of a deletion of a 5–6 Mb region, in approximately 20–30% of cases, it is due to maternal uniparental disomy, and in 1–4% of cases, it is due to a mutation, deletion, or other defect in the imprinting center. PWS and its sister syndrome, Angelman syndrome, were the first examples of genetic imprinting in humans.

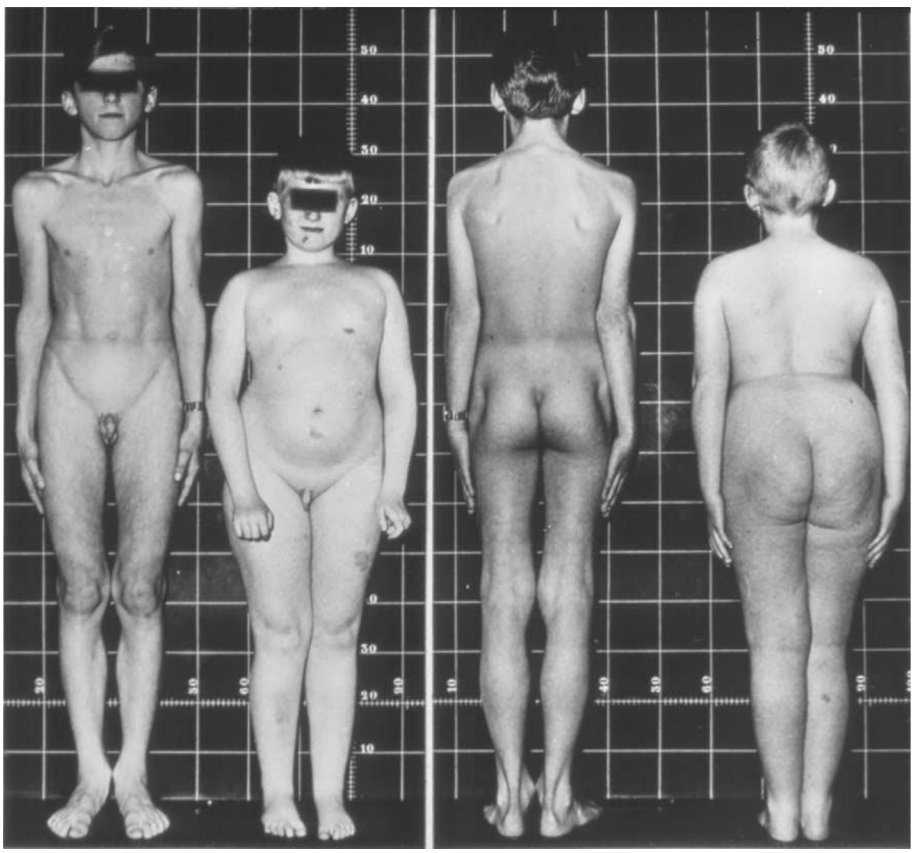

Fig. 1 Original photo of twins by Prader: in each photograph, the boy with PWS is on the right and the healthy boy is on the left.

Clinical picture

Hypotonia

The clinical picture of PWS changes with age. Neonates present with severe hypotonia (Fig. 2), poor reflexes and a weak or absent cry. During the first weeks or even months, infants with PWS have severe feeding difficulties and require special feeding techniques, in most cases nasogastric tubes. Underweight due to poor sucking and swallowing reflexes is a characteristic feature in infancy. Usually in these days, PWS is diagnosed early after birth due to the severe hypotonia.

Obesity

Between the second year of life and the fourth year of life, obesity sets in as a consequence of uncontrolled compulsive eating due to the PWS-specific increased appetite or lack of satiation respectively, reduced energy expenditure and decreased physical activity. Distribution of subcutaneous fat is shifted towards the trunk, with relative sparing of the distal extremities. In contrast to non-syndromic obesity, increased fat mass in PWS is accompanied by a decrease in lean body mass.

Short stature

Growth is characterized by moderate intrauterine and postnatal growth delay, slight to moderate delay of bone maturation, lack of a pubertal growth spurt and short stature as an adult. In the absence of growth hormone replacement, males grow to an average adult height of 161.6 ± 8.1 cm and females to an average height of 151.1 ± 5.5 cm. In some individuals, scoliosis, as well as osteopenia and osteoporosis, may be present.

Hypogonadism

Genital hypoplasia is present in both sexes. Boys usually present with a small penis, cryptorchidism and a bifid or hypoplastic scrotum. In females, clitoral and labia minora hypoplasia is usually found. In most cases, pubertal development of the gonadal axis is delayed, insufficient or absent, more so in boys than in girls. No cases of paternity have been reported in PWS, but four pregnancies have been documented in females with PWS. These four resulted in two normal off-springs and two off-springs with Angelman syndrome.

Developmental delay and mental retardation

Developmental delay is a major concern in most cases. In particular, speech and motor development are retarded. Speech and language difficulties become apparent from an early age on. Children with PWS usually are able to sit upright at 12 months, walk between the ages of 28 and 32 months and talk in short sentences as late as at 42 months. Most people with PWS have mild to moderate mental retardation and IQ tests indicate an average IQ of around 60–70.

Behavioral problems

During early childhood, a characteristic behavior profile emerges. Even at this early stage, young children typically stick to an activity with more persistence than other children and have difficulties with changes in routine. Nevertheless, younger children are happy, affectionate and cooperative. After the age of 2 years, children with PWS may become obsessed with food and later develop all kinds of food-seeking strategies and atypical behavior, such as gorging on available food, breaking into locked food storage areas and getting up

Fig. 2 Severe muscle hypotonia in an infant with PWS.

at night to forage for food. By the time they reach school age, the compulsiveness and obsession of their behavior become more evident. Typical temper tantrums are often observed. Stubbornness and intolerance of frustration relates in the beginning primarily to withholding of food but may occur also in other situations at a later stage, especially when they feel under pressure and are afraid of not meeting the demands of parents or teachers or simply because of changes in the daily routine. Skin picking may also be present in such situations. Adolescents are usually described as being extremely stubborn, clever, manipulative, moody and prone to temper tantrums. The prevalence of psychotic illness is markedly increased and can develop in adolescents and adults. It affects more PWS patients with UPD or the imprinting center defect form of PWS (Soni, 2008). Psychotic illness will often present rapidly but can also develop insidiously with a marked deterioration in mood and behavior and requires psychiatric assessment. Medication should be prescribed based on a diagnosed psychotic illness. It is important to start with lower than normal doses and to increase the dose carefully if necessary. Actually, in PWS, risperidone and aripiprazole are the mostly used antipsychotic drugs in PWS.

Respiratory abnormalities

Respiratory abnormalities in PWS are well known (Duis, 2022). An increased incidence of sleep-related breathing disorders has been reported in obese adults with PWS and a primary disturbance of central respiratory control has been demonstrated in young, not yet obese, children with PWS. The pathogenesis of respiratory problems appears to be multifactorial, including central and peripheral mechanisms such as adenoid and tonsil hyperplasia, facial dysmorphism and muscular hypotonia, as well as hypothalamic and chemoreceptor dysfunction resulting in central and obstructive apneas.

Miscellaneous characteristics

Individuals with PWS have a characteristic face with a narrow bifrontal diameter, almond-shaped eyes, strabismus and a triangular mouth. Many individuals with a deletion within the chromosome 15 are hypopigmented with fair hair and blue eyes. Oral characteristics include thick saliva, hypoplastic enamel and caries. Pain sensitivity is reduced and a tendency to self-injury is observed, especially skin-picking on arms, hands and feet. PWS children develop characteristic gestures. The reduced sensitivity to pain can mask typical presentations of acute clinical conditions (e.g., acute abdomen, etc.).

Life expectancy

Life expectancy has been prolonged well into adulthood. Whereas complications of morbid obesity, such as type 2 diabetes and cardiac or respiratory deficiencies, have previously doomed affected individuals to an early death. In the past 25 years early diagnosis of the syndrome and quality of medical care of PWS patients have improved significantly. In a so far hopeless situation the treatment option of growth hormone changed the perspectives and quality of life of PWS patients. General care of PWS patients was improved, mainly by avoiding obesity and resultant complications (e.g. diabetes). Today the annual mortality rate of PWS patients is estimated at 1–4% due to obesity-related complications, gastrointestinal perforations, accidental deaths (e.g. traffic accidents) as well as physiological differences unique to PWS (e.g. central respiratory arrest).

Diagnostic criteria

Diagnostic criteria for PWS were first proposed by Holm (1981) and were further developed through a consensus process in Holm (1993). At that time, sophisticated genetic analyses were not yet widely available.

Because diagnosis of PWS can be confirmed by genetic testing, clinical diagnostic criteria should be used more often to raise diagnostic suspicion and prompt testing. Accordingly, revised clinical criteria to help identify appropriate patients for DNA testing for PWS have been suggested by Gunay-Aygun (2001).

Differentiating the underlying molecular mechanism of a PWS diagnosis (i.e., deletion, UPD, ID) is important for genetic counselling, essential for estimating the recurrence risk as well as predicting genotype-phenotype correlation. Traditionally, deletions of 15q11.2q13 were identified either by FISH (fluorescence in situ hybridization) or, later, by chromosomal microarray analysis (CMA) while methylation abnormalities were detected by targeted testing. Today, it is possible to simultaneously assess methylation abnormalities at several 15q11.2q13 loci as well as copy number variants by msMLPA (methylation-specific Multiplex Ligation dependent Probe Amplification). msMLPA has other advantages: it allows to distinguish between type 1 and type 2 deletions, to identify atypical deletions as well as imprinting center and SNORD116 deletions and (in many cases) to detect and quantify mosaicism. If a maternal uniparental disomy (UPD) is suspected, a confirmatory microsatellite analyses of chromosome 15 on the DNA of probands and parents is indicated (Cassidy, 2012).

Metabolism in PWS

Carbohydrate metabolism

Diabetes mellitus is rarely seen in PWS children under the age of 16 years. About 12–25% of adult PWS, however, develop diabetes as a consequence of severe obesity and/or increased familial or ethnic risk for diabetes. Children and adolescents generally present

with low fasting insulin levels and a normal or even increased insulin sensitivity, but a reduced and delayed insulin response of beta cells in oral glucose tolerance tests. However, oral glucose tolerance tests may show an impaired glucose tolerance due to a slower gastrointestinal passage in PWS than in the normal population. Normal insulin sensitivity in PWS seems to be related to the relatively low degree of visceral fat accumulation (Goldstone, 2001). Later, the manifestation of a type 2-like diabetes in PWS is assumed to be precipitated by the addition of excessive obesity to impaired insulin secretion.

Energy balance

The enormous fat accumulation in PWS is caused by an imbalance of energy intake and energy expenditure and a reduced metabolic rate. Patients with PWS have a lower lean body mass which contribute to reduced basal level of energy expenditure. Basal metabolic rate, largely identical to the resting energy expenditure, was found to be decreased by 20% (under growth hormone therapy) to 50% (without growth hormone therapy) in PWS, when related to weight for height, reflecting the decrease in lean mass in this syndrome. Activity-related energy expenditure, assessed by deuterium dilution, is also decreased in PWS. The reason that PWS children and adolescents engage less in physical activity has been ascribed to hypothalamic dysfunction. Hypoactivity with resulting decreased energy expenditure is a large contributor to weight gain in PWS (Butler, 2007).

Hypothalamic dysfunction

Despite in-depth knowledge of the genetic condition in PWS, the final link between the chromosomal disorder and the clinical symptoms remains unclear. Hypothalamic dysfunction, as already originally presumed by Prader et al., appears to underlie many of the features of PWS, including hormonal dysfunction, disturbed energy balance, temperature regulation, high pain threshold and sleep disorders, but no overt structural abnormalities of the hypothalamus have been found yet. It has been shown that growth hormone deficiency due to hypothalamic dysregulation contributes not only to the abnormal growth pattern and osteopenia, but also to the excess of body fat and to the deficit of lean body mass with reduced energy expenditure as a consequence. The decreased growth hormone secretion in PWS differs from that seen in simple obesity, where GH secretion is not disturbed, but rather down-regulated and fully reversible by weight loss. Also hypogonadism has been classically thought to be hypothalamic in etiology. Recent evidence supports primary gonadal failure as a significant contributor to male hypogonadism (Noordam, 2021). The pattern of gonadal dysfunction in females seems to be similar to those observed in males. In most cases, pubertal development of the gonadal axis is delayed, insufficient or absent, more so in boys than in girls. Precocious development of pubic and axillary hair, however, is a frequent (15–30%) finding. It is the consequence of premature secretion of adrenal androgens. Single cases with complete precocious puberty are reported in boys with adult testicular volumes and in girls with menarche and may be linked to loss-of-function variations in the MKRN3 gene which is located in the critical region of PWS. Abnormalities in the hypothalamic satiety center and its hormonal circuitry, including orexigenic and anorexigenic gut hormones have been suggested to affect food intake and energy expenditure. The orexigenic plasma Ghrelin is increased in obese PWS individuals compared to any other form of obesity and was supposed to contribute to the hyperphagia of PWS. The studies of other hormones, especially the anorexigenic gut hormones GLP-1 or PYY gave disappointing results. In recent years, the hypothalamic hormone oxytocin has emerged as a candidate not only for improving social behavior but also for potentially positively affecting hyperphagia in Prader-Willi syndrome (PWS). However, subsequent studies in children and adults with PWS have yielded conflicting results, with some patients showing improvements and others showing no change or even worsening of symptoms. This variability has dampened initial optimism and underscored the need for a more nuanced understanding of oxytocin's effects on both appetite regulation and behavior. The most promising results with intranasal oxytocin have been obtained in either infants, toddlers or young children, suggesting that early treatment is most likely to be successful (Tauber, 2017).

Therapy

Comprehensive team approach

Children and adolescents with PWS need a variety of interventions to optimize their growth and development. This includes physical and occupational therapies, dietary management, GH and sex steroid substitution, speech and learning disability services, behavioral and family interaction management, support and care. We call this the five-finger model. The five-finger model includes

1. Calorie restriction with the aim of maintaining weight for height in the upper normal range for age and sex.
2. Growth Hormone Therapy as soon as possible after confirmation of the diagnosis.
3. Daily physical training with physiotherapists, parents and caregivers.
4. Sex hormone replacement, generally starting in boys at a bone age of 13 years and in girls at a bone age of 11 years if puberty does not start spontaneously or later in case of a pubertal arrest.
5. Family coaching and case management supporting parents in all aspects of PWS including social, psychological, school, home and insurance questions.

Other specialists may also be needed, such as an orthopedic surgeon in the case of scoliosis (which affects more than 40% of children and adults with PWS). Adolescents with PWS also go through a period of detachment. On the way to school or work, parents' ability to supervise is limited and possibilities of uncontrolled food acquisition are increased. Moving out of the parental home and into a home with other adults helps people with PWS to grow up, gain a certain degree of independence and take on new responsibilities and rights. Much depends on the home and the caregivers. Many of those affected now gain weight and obesity and its consequences come to the fore, with problems such as diabetes and obstructive sleep apnea syndrome (OSAS) with daytime sleepiness, night-time snoring, etc.

Sexual activity is usually severely restricted. Nevertheless, contraception is very important, as women with PWS in particular can easily be seduced by food offers.

Dietary restriction

Children with PWS must stick to a strict diet with a reduced energy intake of about 75% of that for healthy children to stabilize the weight balance. A food intake restriction of this extent is possible only with close and strict supervision by parents and caregivers. Instead of counting calories, it is usually easier to check weight every week and to adjust caloric intake to the weight evolution. Consequently, there is a lifelong need for environmental modifications to restrain food intake in PWS. Growth hormone treatment makes weight control easier increasing physical activity, muscle mass and caloric output.

GLP-1 receptor agonists

The idea of using glucagon-like peptide-1 receptor agonists (GLP1 agonists) in patients with PWS is straightforward. However, the first available study results are disillusioning and currently speak against such an approach (Diene, 2022).

Growth hormone treatment

Growth hormone therapy in PWS was initiated in the 1990s. In prepubertal obese children with PWS, administration of GH has a remarkable impact on growth and, in combination with restriction of food intake, also on body composition, resulting in a dramatic change in the phenotype. GH treatment increases height velocity and normalizes growth and body proportions. Some studies show a better effect when Growth hormone therapy is started before the age of 2 years (Eiholzer, 2004). It is recommended to start the treatment therefore as soon as the diagnosis is assured. Growth hormone dosage is the same as in growth hormone deficiency (i.e., 0.7–1.0 mg/m^2/d) and due to obesity is calculated rather according to body surface area than according to weight (Deal, 2013). If treatment is instituted early enough, final height prediction will reach the parental target height range after 3 years and short stature as well as small hands will no longer be present. Small feet however will catch up only partially, probably because of low physical activity. The adult height generally is around −1 SDS of familial target height (Angulo, 2015). GH has a sustained impact on the net loss of body fat, which nevertheless remains elevated, and improves the pattern of serum lipids (Carrel, 2010). In addition to the medical benefits, the disappearance of the obese phenotype of prepubertally GH-treated PWS children relieves the patients and their families of stigmatization. A further benefit of GH treatment in PWS is the increase in lean body mass and, subsequently, resting energy expenditure. This leads to a reduction of energy stores, mainly of body fat, if energy intake is not increased. However, the initial deficit in lean body mass is counteracted by GH only during the first year of therapy. In the long term, GH therapy does not further compensate for this deficit, probably because of reduced physical activity. Further favorable effects of GH treatment in PWS were reported on respiratory muscle function, physical capacity, strength, agility and activity. There are reports of PWS deaths shortly after initiation of growth hormone therapy due to respiratory insufficiency. The question was raised if the growth hormone therapy was the cause of these deaths and after these deaths, polysomnography was usually done before the growth hormone therapy was started. In one case, a child died during the night after a normal polysomnography without ever having received growth hormone therapy. PWS itself is therefore thought to be a risk factor for sudden death, as hypothalamic dysfunction can lead to respiratory disorders and disturbed sleep architecture (e.g. altered REM sleep latency). This can result in both central and obstructive sleep apnea with desaturation, the latter of which may also be associated with obesity and enlarged adenoids and tonsils. All this can increase the risk of respiratory failure in early childhood and also later in life lead to pronounced narcolepsy-like daytime sleepiness. Polysomnography should be performed when starting GH treatment, but should not delay the start of GH treatment. In addition, the child should not have a respiratory infection at the time of starting GH therapy. The following aspects should always be asked at follow-up visits: observed breathing patterns, narcolepsy-like symptoms, insomnia, cataplexy and excessive daytime sleepiness.

There is likely no correlation between the start of treatment with GH and the onset or severity of a scoliosis. However, scoliosis or kyphosis are exacerbated during periods of rapid growth and require careful orthopedic management. Spinal surgery in patients with PWS is associated with a high risk of complications. A conservative approach is therefore clearly preferable whenever possible (van Bosse, 2020).

Physical therapy and exercise

Children with PWS have decreased muscle tone and a deep dislike for physical activity. Decreased muscle mass is a consequence of physical hypoactivity (Eiholzer, 2003). It should therefore be the aim of parents, caregivers and physiotherapists to improve

physical activity at a maximum. Physical activity should get the same attention as the reduction of food intake. Physical activity should aim to improve muscle strength and overall physical fitness and as well to prevent scoliosis. Increased physical activity may lead to increased energy expenditure, it promotes a negative energy balance, raises the postexercise metabolic rate, builds muscle mass, and enhances the overall sense of wellbeing. Therefore, the crucial importance of regular physical activity should be clearly communicated to patients, parents, and caregivers.

Sex hormone substitution

Hypogonadism is well documented in PWS and sex steroids are known to benefit muscle mass and bone health (Eiholzer, 2021). However, there is no consensus on the most appropriate regimen for sex hormone treatment in PWS. Most experts recommend androgen substitution in men because of its beneficial effects, such as complete virilization, voice change, osteoporosis prevention, and increased muscle mass and activity levels. Some concerns remain about the potential for increased aggressive behavior and temper tantrums. One study examining behavior during sex steroid substitution did not reveal any differences between PWS and their siblings. However, it seems reasonable to start as low as 25% of the recommended normal adult testosterone enanthate dose (250 mg per month) with gradual increase as tolerated to keep low normal serum testosterone levels. Adult males are treated with testosterone undecanoate (750–1000 mg every 3 month).

Despite growth hormone treatment, muscle mass remains low in PWS. Timely testosterone substitution is crucial for boys with PWS to achieve optimal muscle mass, albeit lower than average. It is started in boys generally at a bone age of 13 years if puberty does not start spontaneously or later in case of a pubertal arrest. During the first 3–4 years of puberty, muscle mass increases normally in males with PWS, whether puberty occurs spontaneously (in about 30%) or is induced by exogenous testosterone (Noordam, 2023). Muscle mass is strongly correlated with bone mass, suggesting that testosterone replacement improves bone mass development. Increased muscle mass positively impacts energy balance, physical activity, insulin sensitivity, and cardiovascular health.

In young women with PWS, estrogenic substitution may prevent osteoporosis and although an increase in obesity is feared, it has not yet been scientifically assessed in these patients. Guidelines for hormone replacement therapy in PWS are tailored individually depending on sex development, hormonal profiles, bone density and emotional and social needs.

Family coaching and case management

Successful patient management requires a multidisciplinary team. It is important to empower the family to use their own resources and support should be provided when family resources are exhausted. The chorus of specialists should be led by a leader, a specialist and expert in the various aspects of PWS. It must be kept in mind that each specialist tends to have a tunnel vision of the patient and it is important to keep an overall picture of the child. However, the focus must always be on the wellbeing of the whole family, father, mother and siblings.

Summary

Prader-Willi Syndrome is a complex genetic disorder primarily marked by obesity, growth impairment and behavioral issues due to hormonal imbalances. Early diagnosis and a multidisciplinary approach—focused on growth and sex hormone therapy, dietary management, and structured behavioral support—are key to improving both life expectancy and quality of life. The persistent hyperphagia creates a need for strict supervision, making an independent living impossible.

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