Prader-Willi Syndrome

Extract from: Encyclopedia of Endocrine Diseases, 2nd Edition/ 2018
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Glossary

hypogonadism Decreased or non-existent hormone secretion by the gonads. The gonads refer to both sex glands, the female ovaries and the male testes.

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

hypotonia Decreased muscle tone, generally in an infant. There is a rag doll-like feeling or sense of floppiness on holding the infant.

obesity Excess body weight, defined as a body mass index over 30 kg/m^2 in adults or, in children, above the 90th or 97th percentile of normal references.

Prader-Willi syndrome is a complex neurogenetic disorder and the most common genetic cause of obesity.

INTRODUCTION

Prader-Willi syndrome (PWS) was first described in 1956 in Zurich by Andrea Prader, Alexis Labhart, and Heinrich Willi. 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 centre. PWS and its sister syndrome, Angelman's syndrome, were the first examples of genetic imprinting in humans.

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 and fourth years 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 toward 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 ± 8.1cm and females to an average of 151.1 ±5.5cm. 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 4 pregnancies have been documented in females with PWS. These 4 resulted in 2 normal off-springs and 2 off-springs with Angelmann 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 up at 12 months, walk between the ages of 28 and 32 months, and talk in short sentences as late as at 42 months. Most Individuals with PWS present mild to moderate mental retardation and IQ testing indicates an average IQ of approximately 60 to 70.

Behavioural Problems

During early childhood, a characteristic behaviour profile emerges. Even at this early stage, young children typically stick to an activity with more persistence than other children and have difficulty 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 behaviour, such as gorging on available food, breaking into locked food storage areas, and getting up at night to forage for food. By the time they reach school age, the compulsiveness and obsession of their behaviour 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 specially when they feel under pressure and are afraid of not meeting the demands of parents or teachers or simply because of changes in daily routine. In such situations skin picking may also be present. Adolescents are usually described as extraordinarily stubborn, clever, manipulative, moody, and prone to temper outbursts. Prevalence of psychotic illness is markedly elevated and may develop in adolescents and adults. It affects more PWS patients with UPD or the imprinting centre defect form of PWS. Psychotic illness will often present rapidly but can also develop insidiously with a marked deterioration in mood and behaviour and requires psychiatric assessment. Medication should be prescribed based on a diagnosed psychotic

illness. It is important starting with lower than normal doses increasing 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. 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 seems to be multifactorial in origin, including peripheral and central mechanisms, such as muscular hypotonia and facial dysmorphism as well as hypothalamic and chemoreceptor dysfunction.

Miscellaneous Characteristics

Individuals with PWS have a characteristic face with a narrow bifrontal diameter, almond-shaped eyes, strabismus, and a triangular mouth. Many individuals 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.

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 fifteen 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 in 1981 and were further developed through a consensus process in 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-Algun et al. The differential DNA methylation of several imprinted maternal and paternal loci in the 15q11.2-q13 region provides a powerful tool for assessing paternal-only, maternal-only and biparental inheritance. However DNA methylation cannot distinguish the molecular classes (deletion, UPD, ID), which is important for genetic counselling and genotype-phenotype correlation. Deletions of 15q11.2-q13 have traditionally been diagnosed with chromosomal analysis using FISH (fluorescence in situ hybridization). With the increasing use of CMA (chromosomal microarray) in clinical genetics, this technique might replace FISH someday as CMA will precisely report the deletion size. If DNA methylation is positive for PWS but no deletion is found, the next step is to distinguish between maternal uniparental disomy (UPD) and imprinting defect (ID) which is done by using DNA polymorphism analysis of chromosome 15 loci on the proband`s and parent`s DNA.

METABOLISM IN PWS

Carbohydrate Metabolism

Diabetes mellitus is only rarely seen in PWS children under the age of 16 years. About 15% 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. 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.

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 (GH) secretion in PWS differs from that seen in simple obesity, where GH secretion is not disturbed, but rather is down-regulated and fully reversible by weight loss. Also hypogonadism has been classically thought to be hypothalamic in aetiology. Recent evidence supports primary gonadal failure as a significant contributor to male hypogonadism. 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. 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 these days, the hypothalamic hormone Oxytocin became a candidate to improve not only social behavior but possibly also to influence positively hyperphagia in PWS. The first trials with children and adults with PWS however gave conflicting results, improving social interaction, temper tantrums as well as hyperphagia in some patients and worsening these symptoms in others. Longer term studies in different age groups and with different dosages are needed and will certainly be done in the nearest future.

THERAPY

Comprehensive Team Approach

Individuals 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, language and learning disability services, behaviour and family interaction management, support, and care. We call it the five-finger model. The five-finger model includes 1. Restriction of caloric intake aiming to keep 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 or after of confirmation of growth hormone deficiency by clinical and laboratory tests. 3. Daily physical training conducted by physiotherapists, parents and caregivers. 4. Sex hormone replacement, starting in boys generally at a bone age of 13 years and in girls at a bone age of 11 years if puberty does not start spontaneously. 5. Family coaching and case management supporting parents in all aspects of PWS including social, school, home and insurance questions.

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.

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. 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. 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 and feet will no longer be present. The adult height generally is around -1 SDS of familial target height. GH has a sustained impact on the net loss of body fat, which nevertheless remains elevated and improves the pattern of serum lipids. 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 favourable 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 initiation of growth hormone therapy. However, one child died the night after a normal polysomnography, i.e. the child had not received growth hormone therapy yet. This demonstrates that PWS itself is a risk factor for sudden death. But because an increased risk of respiratory failure in the first three months of growth hormone therapy cannot be definitely excluded, a polysomnography should always be performed before initiation of growth hormone treatment. Furthermore, at initiation of growth hormone therapy the child must not have a respiratory tract infection. Scoliosis or kyphosis can be aggravated during phases of fast growth and requires careful orthopaedic management.

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. 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 post-exercise 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

Although hypogonadism is clearly documented in PWS, and the beneficial effect of sex steroids on the muscle mass and bone health is well known, no consensus statement exists as to the most appropriate regime of sex hormone treatment in PWS. Most authors recommend androgen substitution in males because of its beneficial effects, such as complete virilization, change in voice, prevention of osteoporosis, and increasing muscle mass as well as activity level, but some authors believe that it may lead to a more aggressive behaviour and aggravate temper tantrums. One study examining behaviour 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 (200-250mg) with gradual increase as tolerated to keep low normal serum testosterone levels. 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 hormonal replacement therapy in are tailored individually depending on sexual 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 allow the family to use their own resources, support should set in only when family resources are exhausted. A leader, a specialist and expert in the different aspects of PWS should conduct the chorus of the different specialists. It must be considered that each specialist tends to have a tunnel vision of the patient and it is important to keep a general picture of the child.