Prader-Willi syndrome

What is Prader-Willi syndrome?

Prader-Willi syndrome (PWS) is a neurodevelopmental genetic disorder. The main features include infantile hypotonia, a poor suck, failure to thrive and hypogonadism/hypogenitalism. Short stature and small hands/feet due to growth and other hormone deficiencies, hyperphagia and marked obesity occur in early childhood. Cognitive and behavioural problems (tantrums, compulsions, compulsive skin picking) are common [1] .

Prader-Willi syndrome genetics

Prader-Willi syndrome was the first human disorder attributed to genomic imprinting. It is caused by lack of expression of genes inherited from the paternal chromosome 15q11-q13 region due to [1] :

- Paternal 15q11-q13 deletions (about 60%); or
- Maternal uniparental disomy 15 or both 15s from the mother (about 35%).

The opposite, ie maternal deletion or paternal uniparental disomy, causes Angelman's syndrome.

Prader-Willi syndrome epidemiology [1]

- The estimated prevalence is 1 in 10,000 to 20,000 individuals with a reported range of 1 in 8,000 to 1 in 30,000.
- Most cases of PWS are sporadic with an approximate 1:1 gender ratio. All ethnic groups are represented, but PWS is reported to be disproportionately more in Caucasians.
- Prader-Willi syndrome is the most common known genetic cause of life-threatening obesity in humans.

Diagnostic criteria[2]

As diagnostic tests are now available these should serve to raise suspicion and ensure that all appropriate people are tested, but avoid the expense and worry of unnecessary testing.

- From birth to age 3 requires 5 points including 4 major criteria.
- Age 3 to adult requires 8 total points including 5 major criteria.

Major criteria (1 point each):

- Neonatal or infantile central hypotonia with a poor suck. This gradually improves with age.
- Feeding problems in infancy or failure to thrive.
- Excessive weight gain between 1 and 6 years of age. Morphological and hormonal abnormalities of the pituitary gland are found in PWS[3] . Marked differences in obesity have been found between patients living in different countries. It is thought that these differences could be explained by differences in management[4] .
- Characteristic facial features (narrow face, almond-shaped eyes, etc).
- Hypogonadism - genital hypoplasia and/or delayed or incomplete gonadal maturation (this is not always associated with infertility in boys)[5] .
- Cryptorchidism is common.
- Global developmental delay (in a child aged <6 years). They may not sit until 12 months, or walk until 24 months. Older children show mild-to-moderate learning difficulties and an IQ of 50 to 70.
- Hyperphagia with excessive appetite or food obsession.
- Chromosomal abnormality - deletion 15q 11-13 or other appropriate molecular abnormality in this chromosomal region.

Minor criteria (0.5 points each):

- Decreased fetal movements, infantile lethargy or weak cry in infancy, which improves with age.
- Characteristic behavioural problems (typically tantrums or obsessive/compulsive behaviour)[6] . Adults may have psychotic episodes.
- Sleep disturbance/sleep apnoea.
- Short stature in childhood and failure of pubertal growth spurt.
- Hypopigmentation - fair skin and hair.
- Small hands and feet.
- Narrow hands with straight ulnar border.
- Eye abnormalities (esotropia, myopia).
- Thick, viscous saliva ± crusting at mouth corners.
- Speech articulation defects.
- Skin picking.

Other features of Prader-Willi syndrome which may be present, many of them related to problems of the hypothalamus:

- High pain threshold.
- Decreased vomiting.
- Temperature instability or altered temperature sensitivity.
- Scoliosis or kyphosis (66.7% at skeletal maturity in one series of 145 patients)[7] .
- Early adrenarche (pubic or axillary hair before age 8) despite retardation of other sexual development.
- Obesity may cause type 2 diabetes at an early age, also called 'maturity onset diabetes of the young' (MODY).
- Osteoporosis (because of hypogonadism). Along with a high pain threshold this can lead to pathological fractures that are not instantly recognised.
- They display an unusual skill with jigsaw puzzles[8] .

- IQ is usually in the range of 60 to 80 but with expected individual variation. Genetic subtypes of the condition have differing IQ strengths - verbal vs performance IQ[9] .

PWS patients have a different gait from individuals who are simply obese[10] .

Prader-Willi syndrome symptoms[11]

- Clinical features change with age with hypotonia and a poor suck resulting in failure to thrive during infancy.
- As the child gets older, other features such as short stature, food seeking with excessive weight gain, developmental delay, cognitive disability and behavioural problems become evident.
- The phenotype is likely due to hypothalamic dysfunction, which is responsible for hyperphagia, temperature instability, high pain threshold, hypersomnia and multiple endocrine abnormalities including growth hormone and thyroid-stimulating hormone deficiencies, hypogonadism and central adrenal insufficiency.
- Obesity and its complications are the major causes of morbidity and mortality in PWS.

Therefore the clinical presentation may be seen in two stages:

- After birth there is hypotonia, failure to thrive and sleepiness. The child usually has blue eyes and blond hair. They tend to lag behind other children in the transition to solid food.
- The second stage becomes apparent at the age of 12-18 months, when an exceptional interest in food becomes apparent[6] . Hyperphagia, obesity, hypogonadism, short stature and sleep apnoea and cor pulmonale occur. They have markedly elevated levels of ghrelin, a hormone associated with hunger[12] .

Prader-Willi syndrome diagnosis[13]

DNA methylation analysis and fluorescent in situ hybridisation (FISH) techniques can diagnose PWS in all three types of PWS, as well as differentiate PWS from Angelman's syndrome in deletion cases[14]

Monitoring and screening for endocrinopathies are recommended, particularly growth hormone deficiency, hypogonadism, hypothyroidism, central adrenal insufficiency and bone health/vitamin D deficiency.

It is recommended to obtain HbA1c, lipids and transaminases in all patients at the age of puberty, and then annually if obese. HbA1c should be checked annually for all those with PWS treated with GH therapy.

Psychological and/or educational testing is also required.

Differential diagnosis

- Obesity.
- Fragile X syndrome.
- Cryptorchidism.
- Short stature.
- Hyperphagic short stature syndrome.

Prader-Willi syndrome treatment and management[13]

Treatment of Prader-Willi syndrome consists of intensive rehabilitation, psychological care, speech therapy and also, if the appropriate criteria are fulfilled, growth hormone treatment. An extremely important part of management is also properly planned and implemented nutritional management to prevent malnutrition in the first stage of life and the development of excessive weight in subsequent years[15] [16] .

A multidisciplinary approach is essential:

- Family support is essential to cope with the behavioural difficulties throughout childhood. The child must be kept away from excessive food intake, to guard against subsequent obesity[17] . Their energy requirements are only about 75% of that of a normal child and hyperphagia can occasionally be dangerous, causing massive stomach dilation. Regular exercise is important.

- Input from a paediatric gastroenterologist, endocrinologist, psychologist, psychiatrist, dietician, occupational therapists, speech therapists, exercise advisors and orthopaedic consultants may be helpful. Bariatric surgery has had poor results compared with normal, obese adolescents [18] .
- Management of the transition period from childhood to adulthood is important and placement in a residential home may need to be considered [19] . The GP will continue to provide care throughout the transition and during adulthood. Specific points related to PWS to consider during a health check include:

    - Sleep apnoea (obstructive, central or mixed) - even where obesity is not a problem.
    - Scoliosis, kyphosis.
    - Osteoporosis.
    - Oedema.
    - Cellulitis.
    - Hypothyroidism.
    - Gastroparesis.
    - Type 2 diabetes.
    - Skin infections (consequence of skin-picking).
    - Squint, myopia.

Pharmacological

- Growth hormone is essential to maintain normal growth, and muscle development, and to avoid obesity [20] . Growth hormone treatment was initially thought to make scoliosis worse but this has been refuted [21] .
- Appetite suppressant drugs are of no value. Long-acting octreotide reduces ghrelin secretion but does not affect behaviour or weight [22] .

- Many drugs have been used to modify behaviour but they tend to be ineffective or even counterproductive. Olanzapine may have an effect.
- Haloperidol and fluoxetine are sometimes effective.
- Selective serotonin reuptake inhibitors (SSRIs) seem to have a nonspecific behaviour-stabilising effect, with fewer outbursts, a marked reduction in irritability and less perseveration but with no antidepressant effect.
- All these drugs may be tried with care. None is universally successful and they may even be counterproductive.

Genetic counselling

Recurrence risk depends on the mechanism causing PWS in the individual:

- Deletion is sporadic and has a recurrence rate of ≤1% (except in the rare cases where a chromosomal rearrangement is present in the father).
- Maternal uniparental disomy 15 is typically de novo also with a recurrence rate of ≤1% (except if a Robertsonian translocation is present in either parent).
- A proportion of those with an imprinting defect have a microdeletion in the imprinting centre; this can be familial and has a 50% recurrence risk when it is. However, the greater proportion of those with an imprinting defect have an epigenetic mutation and the recurrence risk is ≤1% for this group.

Prognosis[1]

Based on population studies, the death rate in PWS is estimated at 3% per year.

In a large survey of causes of death in PWS:

- The most common causes were respiratory failure (31%), cardiac (16%), gastrointestinal (10%), infection (9%), obesity (7%), pulmonary embolism (7%), choking (6%) and accidents (6%).

- The average age of death in the 486 individuals with PWS reported in 2017 was 29.5 years. 80% of those who died were older than 18 years of age.

Further reading

- International Prader-Willi Syndrome Organisation
- Prader-Willi Syndrome Association UK
- Fermin Gutierrez MA, Mendez MD; Prader-Willi Syndrome. StatPearls, Aug 2021.

Authored by:	Peer Reviewed by: Dr Laurence Knott	
Originally Published: 20/11/2023	Next review date: 17/12/2021	Document ID: doc_2649

View this article online at: patient.info/doctor/prader-willi-syndrome-pro

Discuss Prader-Willi syndrome and find more trusted resources at Patient.