# Prader–Willi syndrome: clinical features and management

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**Abstract**

Prader Willi syndrome is a rare genetic disorder associated with extreme obesity, short stature, and learning disability. There is a characteristic behavioural phenotype. Understanding of the genetic mechanisms has expanded in recent years as new laboratory techniques have been developed. Nowadays the clinical diagnosis is normally made in infancy. Management focuses on improving nutrition in the early months, then restricting calories to limit rapid weight gain. Several endocrine problems are encountered and these are discussed. There is increasing experience of growth-hormone therapy both to increase longitudinal growth but also to improve body composition and possibly improve mobility.

**Keywords** growth hormone; hyperphagia; obesity; Prader–Willi syndrome

## Introduction

Prader–Willi syndrome (PWS) is a rare genetic condition that was described more than 50 years ago in Switzerland by Prader, Labhart and Willi. Affected children have severe obesity, short stature, learning disability and other characteristics described below. There are somewhat variable figures for the incidence, which is approximately 1 in 10,000 new births, and this is due to incomplete ascertainment in some studies.

## Genetics

The genetic defect arises in seven genes which are situated on chromosome 15 q11–13 region; some or all of these genes are either missing or not expressed on the paternal chromosome. The disorder is attributed to genomic imprinting whereby the genes are expressed differently depending on the parental origin of the missing genomic material on the *paternal* chromosome 15. Angelman syndrome, which has a totally different phenotype (sometimes referred to as the happy puppet syndrome), results from loss of *maternal* genomic material at exactly the same site on the chromosome.

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The condition appears to be sporadic rather than inherited in a Mendelian pattern. There is no gender difference in incidence, and the condition occurs in all races. The genes responsible must encode proteins which are responsible for normal brain development and specifically for function of the hypothalamic area. In the majority of cases (56–75%) there is a paternal deletion on the long arm of chromosome 15 in the q11–15 region. Approximately 25% of cases are due to maternal uniparental disomy caused by chromosome non-disjunction, so two copies of the maternal chromosome 15 are present and consequently there are no paternally expressed genes. Approximately 1% of cases are due to an imprinting error, and lastly less than 1% of cases are due to a paternal chromosome translocation.

## Clinical presentation and diagnosis

PWS frequently presents in the newborn period with severe hypotonia and floppiness, and these symptoms may be present even if the infant is born prematurely. Head lag may be profound, and there will be poor muscle tone in the shoulder girdle. The infant tends to slip through an examiner's hands when being held around the trunk. The differential diagnosis includes other neurological conditions such as myotonic dystrophy, myasthenia gravis, spinal muscular atrophy type 1 (Werdnig–Hoffmann disease), or severe hypoxic ischaemic encephalopathy..

A history of feeding difficulties is very typical. These infants may well be slow with bottle feeding in the first month of life and often require gastric tube feeding. The suck reflex is reduced, and when tube feeding ceases there is often a history of slow weight gain with faltering growth. Neonates will often have an unusual facial appearance. In the newborn period PWS is frequently confused with other conditions such as Down's or Turner's syndromes. Cryptorchidism is present in 80% or so of affected boys (see below).

During infancy features of mild to moderate global developmental delay will be noted, and motor development may be especially delayed with quite late walking. Growth measurements show short stature with length below predicted centiles during the first 2 years of life, and height is frequently between the 0.4th and 9th centile on a standard growth chart. Weight gain often remains slow until features of excessive appetite develop, and this is usually between 1 and 2 years of age when a rapid increase is seen over a period of several months, with rapid crossing of centiles on the growth chart. If calorie restriction is not undertaken rapidly at this stage the young child with PWS will develop severe obesity.

Children presenting at a later age whilst at primary school will have some degree of learning disability. There will be an obsession with food and a vast appetite, and this combined with short stature and severe obesity strongly point to the diagnosis. Sometimes there are specific facial features that help with diagnosis. Today it is unusual for children with PWS to present at a later age, and the typical features at different ages are shown in Table 1.

## Developmental progress

Children with PWS are hypotonic and will have delayed sitting and walking as well as other major motor milestones. Muscle

**Diagnostic features of Prader–Willi syndrome**

| Age | Clinical features |
|---|---|
| Birth to 6 months | Severe hypotonia, failure to thrive, poor feeding, requirement for tube feeding, unusual facial appearance, global developmental delay, thin lips and almond shaped eyes |
| 6 months to 2 years | Initially failure to thrive followed by rapid weight gain at 12–24 months, cryptorchidism, short stature and developmental delay |
| 2–11 years | Short stature, extreme obesity, mild to moderate learning disability, hyperphagia, skin-picking, behavioural issues, scoliosis, sleep apnoea, pale skin and hair compared to others in family |

**Table 1**

strength is reduced, however there is often a gradual improvement in physical strength and function over the first few years. There is some evidence that growth-hormone therapy improves muscle function and increases mobility in children with PWS. Additionally, mild global developmental delay is present, and speech and language therapy input may well be required to improve language development.

It is frequently necessary to involve the use of a child development centre so that multi-agency care can be coordinated. Physiotherapists will give advice and support to parents about motor development. Speech and language therapists will frequently be needed in the early years, and there may need to be support from a teacher counsellor so that early nursery placement and preschool teaching can be optimized. Developmental quotient or intelligence tests carried out later on often show mild to moderate learning disability, so once children with PWS are getting to school age they may need to have assistance in the school setting with a teaching support assistant. Most can remain in normal primary education with such support and backup. Some PWS children will need a statement of educational needs, and a few children will need special schooling with a high teacher-to-pupil ratio from primary school onwards. A higher proportion of children with PWS will need special help at secondary school, and some behavioural psychological issues will usually have developed by this time.

## Cryptorchidism

Undescended testes are present in the majority of boys with PWS; however, the testes may be palpable in the groins and this is due to poor hypothalamic function. The scrotum may be relatively hypoplastic, and the penis appears small. The latter may be because the shaft of the penis is buried in a pubic fat pad, but it is recognized that males with poor pituitary/hypothalamic function can have a micropenis at birth. Infants should be referred to a paediatric surgeon by around 9 months of age, and orchidopexy is performed during the first year or two of life. Most males with PWS are infertile. This is due partly to a hypothalamic gonadotropin deficiency, partly to a primary defect in spermatogenesis arising directly from the chromosomal deletion.

## Obesity

As already discussed, infants with PWS initially have feeding problems and often a relatively slow weight gain. However, at 1–2 years of age there is a sudden increase in appetite, and this coincides with a dramatic increase in the child's weight. The appearance of obesity is exacerbated because children with PWS are relatively short with a height commonly around the second centile. The obesity is central in origin. The cause of the obesity is multifactorial, but one of the main problems is excessive appetite due to disturbance of the hypothalamic appetite centre combined with relative immobility and low calorie requirements. There seems to be no adequate satiation when other individuals would feel full and stop feeding.

As children with PWS become more mobile they tend to forage for food and may eat cat or dog food put out for pets at home. Additionally they start rummaging through rubbish bins to see if food can be found, and as they get older they will often open fridges or cupboards at home to remove food and ingest this in very large quantities. Calorie input may be two or three times that of children of similar age, and a number of behavioural problems may develop at meal times, especially if attempts to restrict food are made. Behavioural eating problems are especially difficult to manage if the child is having school lunch or is visiting other families at home. Short stature and tendency to obesity are exacerbated by growth-hormone deficiency which is hypothalamic in origin and usually partial. Also PWS children have elevated levels of ghrelin which is normally secreted from the stomach and stimulates appetite; high levels of ghrelin are associated with a tendency to obesity. The hyperghrelinaemia precedes the onset of obesity in the first 2 years.

### Management of obesity

Clinical practice guidelines have been developed by a panel of experts in Europe. Children with PWS and their families need specialist input from a paediatric dietician who is used to dealing with such children, and this support will need to be ongoing rather than intermittent. It may also be necessary to have a paediatric psychologist involved to give support and advice about eating and calorie reduction if there are major associated behavioural problems. The aim is primarily to reduce calorie input to about 60% of normal for age, particularly avoiding high-calorie foods which have a high fat content (such as butter, cheese and full-cream milk) but also restricting foods with a high glycaemic index. Careful portion counting is necessary, and practical help and support will be needed about restricting food at home; often advice will be needed about putting locks on fridges and cupboards, and great care will be necessary when the child visits friends and neighbours. Also mealtimes need close supervision, especially at school lunch as children with PWS will tend to overeat and may offer to help eat other children's meals.

Methods of increasing calorie burn-off include regular exercise and activity, and this will be assisted by the improvement in muscle function with growth-hormone therapy (see below).