What is the value of growth hormone therapy in Prader Willi syndrome?

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ABSTRACT

Prader Willi syndrome (PWS) is a genetic condition caused by loss of the paternal copy of a region of imprinted genes on chromosome 15. There is severe muscular hypotonia in the neonatal period, with the onset of hyperphagia and food-seeking behaviour in childhood. All individuals with PWS have developmental delay. Without careful control of food intake and the food environment, individuals with PWS become morbidly obese and are likely to die as young adults from the complications of obesity. The aims of growth hormone (GH) treatment in PWS are distinct from the use of GH in other conditions—although GH does increase final height in PWS, the main benefits of treatment are improved body composition and better exercise capacity, which can help with the aim of preventing obesity. GH trials in PWS have demonstrated improved muscle bulk, reduced fat mass and increased levels of physical activity. GH has also been demonstrated to improve attainment of developmental and cognitive milestones in children with PWS. GH treatment appears to change respiratory status in PWS, possibly because of growth of lymphoid tissue at the start of treatment. Respiratory assessment is recommended prior to, and just after starting GH treatment. Ideal age for starting GH is not clear, although there has been a trend towards starting at younger ages. It may be that GH treatment in childhood confers benefits into adult life. There are less data to support continuing GH treatment into adult life.

Prader Willi syndrome (PWS) is a genetic disorder associated with loss of the paternal copy of a region of chromosome 15, which contains a number of imprinted genes. The commonest genetic cause of PWS is a deletion of this region (65–75% of cases), other causes being maternal chromosomal disomy (20–30%) and abnormalities of the imprinting mechanism. Incidence at birth is reported as 1 : 25–30 000; although there may be an increase over recent years because uniparental disomy is more common in older mothers.[1] The most well-known feature of PWS is increased appetite, but this is only part of the behavioural phenotype. Appropriate management of PWS requires considerable commitment from family and carers to set boundaries around food intake, deal with difficult behaviour, support developmental input and manage associated medical conditions.[2] Box 1 shows the main features of PWS. This article looks at the role of growth hormone (GH) treatment in the management of this complex condition.

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GROWTH AND CLINICAL FEATURES OF PWS

Nowadays, the diagnosis is usually made in the neonatal period, (in contrast with the past when diagnosis was usually delayed until the onset of hyperphagia and obesity). Reduced fetal movements are common. Infants with PWS are profoundly hypotonic at birth and can have respiratory and feeding problems. The poor muscle tone gradually improves but is still present in adult life. There is a wide variation in intellectual outcome, mean IQ is 61 with a reported range of 40–103.[3] Abilities are greater than would be expected for IQ in tasks which require attention to detail, particularly jigsaw puzzles where individuals with PWS score better than normal children of the same age. There are some differences in performance depending on genetic subtype.[4]

Insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP3) are low in PWS,[5] and GH deficiency is common with 40–100% of children fulfilling the criteria for GH deficiency, depending on the test and cut-off level.[6] Significantly reduced lean body mass (LBM), increased fat mass and abdominal adiposity are features of GH deficiency which are shared by PWS. However, GH deficiency is not the only cause of abnormalities in PWS—growth patterns and muscle mass are not completely normalised with treatment and some features, like small hands and feet are not improved.

Growth goes through a number of phases (table 1).[7 8] Birth weight and length are reduced compared with unaffected infants. In the neonatal period, there may be poor length and weight gain, and supplementary feeding is often required.[9] Calorie requirements in PWS are reduced (approximately 60–80% of normal for body weight), and without calorie restriction, excessive weight gain will start before the onset of hyperphagia. Age of onset of hyperphagia is very variable, and it usually continues through adult life although a few adults with PWS reach a point where the appetite is not insatiable. Untreated individuals are short during childhood and have an attenuated pubertal growth spurt, and adult height is reduced compared with midparental height, average 161.6±8.1 cm (standard deviation score (SDS) −2.4) in males and 150.2 ±5.5 cm (SDS −2.5) in females.[10]

PWS is associated with increased risk of scoliosis and hypothyroidism, diabetes risk is greater than expected for weight, and the majority of individuals fail to complete puberty because of a combination of central and gonadal factors.[11] Children with PWS exhibit a range of typical behavioural features; love of routine with repetitive play and conversation, stubbornness, tantrums (which can be very prolonged), and skin picking.

In the past, most individuals with PWS died by their second decade from conditions related to obesity.[12] Families are encouraged to manage the

Box 1 Features of Prader Willi syndrome

Physical features
- Low birth weight
- Short stature
- Small hands and feet
- Characteristic facial appearance with almond-shaped eyes
- Sticky saliva
- Hypopigmentation (in individuals with 15q deletion)
- High pain threshold
- Failure/arrest of pubertal development secondary to central and gonadal factors
- Increased prevalence of hypothyroidism and scoliosis

Neonatal
- Hypotonia and reduced movements
- Undescended testes
- Poor suck, feeding difficulties
- Aspiration and difficulty swallowing fluids
- Developmental delay

Childhood and adolescence
- Hyperphagia (varying age of onset)
- Sleep disturbance, increased prevalence of sleep apnoea
- Stubbornness and tantrums
- Repetitive behaviour and questioning
- Love of routine
- Skin picking
- Skill at puzzles and games (jigsaw puzzles)

Adult life
- Continuing hyperphagia in most cases
- Increased prevalence of diabetes, respiratory problems
- Stubbornness and tantrums
- Possible increased risk of early onset dementia

food environment from the start of life to prevent obesity. If severe obesity is avoided, lifespan is probably normal. For adults with PWS, hyperphagia and behavioural issues continue to have an impact on their lives. Individuals who could otherwise live relatively independently still need supervision of their eating habits, and tantrums and difficult behaviour can put a strain on communal living.[13]

TRIALS OF GH IN PWS

Height outcomes

Studies of GH in PWS were started when recombinant GH became available, initially with height as the endpoint. GH treatment improves height velocity and height SDS during childhood.[14] Long-term treatment with GH increases adult height. In 21 patients treated for an average of 7.9 years with GH, adult height compared with untreated controls was 14 cm taller in females and 17 cm taller in males.[15] Six years of GH treatment, started in infancy and assessed at an average age of 6.7 years in 21 individuals, resulted in an increment in height of 16.9 cm compared with untreated controls.[16] There are no published data on final height after treatment starting in infancy and continuing to the end of growth. Experience in other conditions (such as Turner syndrome) suggests that the extra years of treatment may result in a small increase in height gained. Studies examining the effects of GH on height and growth in PWS found beneficial effects on body composition and exercise capacity; this prompted studies looking at the effects of GH unrelated to height. GH treatment in PWS now aims to improve body composition, exercise capacity and developmental progress, with height gain probably a secondary benefit. There has been a recent publication of consensus guidelines for the use of GH in PWS.[17]

Table 1 Nutritional phases in Prader Willi syndrome

0	Prenatal	Reduced fetal movements and lower birth weight than sibs
1a	0–9 months	Hypotonia with difficulty feeding and decreased appetite
1b	9–25 months	Improved feeding and appetite, growing appropriately
2a	2.1–4.5 years	Weight increasing without appetite increase or excess calories
2b	4.5–8 years	Increased appetite and calories, but can feel full
3	8 years to adulthood	Hyperphagic, rarely feels full
4	Adulthood	Appetite is no longer insatiable

From Miller *et al*[7], Butler *et al*.[8]

Non-height outcomes with GH treatment in PWS

Weight gain, fat, LBM and exercise capacity

Growth hormone is an anabolic agent that increases LBM and decreases fat mass in a range of conditions (and also in healthy individuals). Carrel *et al* reported results for 48 children with PWS treated with GH for 6 years.[14] Treatment started at a mean age of 13±6 months. Compared with an untreated control group of 27 children (mean age 8.2 years), there were significant differences in body fat (36.1% vs 44.6%), and LBM (24.1 kg vs 16.7 kg), in treated versus untreated children. There were beneficial changes in cholesterol profile, and a non-significant rise in fasting insulin in the treated group. Exercise capacity was tested with broad jump, agility run, sit-ups, and upper arm strength assessments; the assessors were blinded to treatment status, and the treated group showed improvements compared to controls in all areas. Other studies have shown a persisting benefit to body fat but not to LBM, compared with ranges for normal children; the natural history of PWS is for increasing fat mass with age compared with normal children, so this probably still represents a benefit.[18 19]

The value of GH treatment would be significantly greater if effects on body composition persisted into adult life after stopping treatment, and there is some evidence that this is the case. In a group of 64 adults, average age 25.4 years (44 treated and 20 not treated with GH as children and adolescents), current weight and Body Mass Index (BMI) were lower by 15% and 21% in the treated compared with the untreated group. There were 2.5 times more non-obese subjects in the GH-treated group, but there was no difference in the prevalence of diabetes, sleep apnoea or in metabolic markers.[20]

There have been studies showing benefit from training and exercise programmes in PWS, but no studies directly comparing this approach with GH.[21] Regular exercise and control of food intake are standard in the management of PWS, so these will be happening for most of the individuals in any GH trial. A possible confounding factor in non-randomised studies is that parents who are more rigorous in their management of food and exercise are also more likely to opt for GH treatment.

Developmental and cognitive outcomes

Measures of development in PWS diverge further from normal children with increasing age. Randomised studies looking at GH treatment in infants and toddlers with PWS found significant improvements in motor development, but also other markers of

development, such as language and cognitive ability.[22 23] A randomised controlled study looking at 50 prepubertal older children, showed that over 2 years, GH treatment prevented the relative deterioration in developmental scores that occurred in the untreated individuals with PWS; after 4 years, GH treatment resulted in an improvement in subscores for abstract verbal reasoning and visuospatial skills.[24] The explanation for the effects on development is not clear, and improved muscle tone does not appear to be the only cause. There may be a direct effect of GH on brain development; studies in other conditions (small for gestational age (SGA), Trisomy 21) have also raised this as a possibility

Adult treatment with GH in PWS

A recent meta analysis of studies of GH in adults with PWS[25] found significant increase in LBM and decrease in fat mass with treatment, no change in BMI and a trend towards higher insulin and insulin resistance in the treated group. Individual studies have also demonstrated improved body composition but no change in bone mineral density.[26] Most adults with PWS are sex steroid deficient (and many are not taking replacement). Sex steroid replacement may contribute to improved body composition in addition to GH.

Complications of GH treatment

Complications of GH treatment reported in other conditions (such as benign intracranial hypertension and local reactions) are probably just as common in PWS although there are limited published data.

Respiratory

Unexpected deaths of individuals with PWS on GH treatment have been reported, apparently related to respiratory causes and obstructive apnoea.[27] Many cases were shortly after starting treatment, and most in individuals who were already obese. It is not possible to directly link GH to the deaths, because similar events are reported in individuals not on GH.[28] Obstructive apnoea in PWS can be caused by hypotonia, large tonsils and adenoids, or obesity.[29] It is speculated that GH increases the bulk of lymphoid tissue in tonsils and adenoids at the start of treatment. Changes in respiratory status in PWS have been reported during GH treatment, so this concern is not unfounded.[30 31] For this reason, there is a recommendation for respiratory assessment before treatment.[17] My current practice is to ask for sleep studies before and after 6–8 weeks of GH treatment. Sleep studies done before GH treatment frequently demonstrate significant abnormalities in children who had no clinical features of sleep apnoea or respiratory issues. Infants with PWS have a high prevalence of central apnoeas, which are not considered a contraindication to GH treatment, and can have both central and obstructive episodes during the same sleep study.[32] Removal of tonsils and/or adenoids, treatment of reflux, or commencement of overnight continuous positive airways pressure (CPAP) may be required prior to starting GH. Children who are significantly obese before treatment are probably more at risk of problems.

Scoliosis

Scoliosis occurs in 25–30% of individuals with PWS. There is no evidence that GH treatment of PWS worsens scoliosis, and it is not considered a contraindication to starting GH.[33] Scoliosis worsens with growth and may progress rapidly in puberty. In most cases, treatment with GH is changing the time course of scoliosis rather than the outcome, but a pause in GH treatment should be considered if there is a rapid deterioration.

Glucose levels

Changes in glucose and insulin levels have been demonstrated at the start of GH treatment,[34] but there is no evidence that GH increases or brings forward risk of diabetes in PWS. Well-controlled diabetes is not considered a contraindication to treatment, although anecdotally diabetes management can be more difficult in the months after starting GH.

When should GH be started?

There has been a trend to start treatment earlier in life, as GH studies have looked at treatment in successively younger children. There are very clear reasons for starting before the onset of obesity, and there are studies showing benefit (body composition and development) from treatment in infancy.[21 22] Recent consensus guidelines suggest starting at 6 months and certainly before 2 years (and some US centres start at 3 months).[17] There is evidence of benefit at the time of treatment in younger children, and some evidence that the benefits of treatment in childhood carry on into young adult life. However, there is currently no evidence that the extra years of treatment generated by starting in infancy translates to a greater benefit later on. Current evidence is probably sufficient to support starting treatment in the first year of life on the basis of the short-term benefits. Practical and financial factors, and the level of concern about respiratory side effects, mean there are wide variations in age of starting.

Assessments prior to starting GH

GH stimulation testing is not mandatory before starting GH treatment,[17] but assessment of respiratory status is required. There has been concern about increased rates of adrenal insufficiency in PWS; tests of cortisol secretion are not required routinely, but vigilance is suggested before and during treatment.

Monitoring and dose adjustment

Continued close supervision of diet and food environment is required and worsening obesity may be a reason to discontinue treatment. Regular monitoring should include vigilance for scoliosis, development of diabetes or hypothyroidism. The current recommendation is to start at a reduced dose (0.015 mg/kg/day or 0.5 mg/m^2/day), repeat the respiratory assessment in the first months of treatment and adjust to a maximum dose of 0.035 mg/kg/day or 1.0 mg/m^2/day.[17] Elevated IGF1 levels have been reported during GH treatment at standard doses, with at least some individuals appearing more sensitive to GH treatment.[35] Because there is a concern that high IGF1 levels might be linked to the risk of side effects, IGF1 should be monitored regularly, and GH doses adjusted to keep the levels at the top of the age-matched normal range (up to +2 SDS).[17]

Transition

A minority of adults are on GH treatment, and the value of continuing GH past final height is not completely clear.[25 26] Consideration of GH treatment in adult life requires GH testing after stopping treatment. GH deficiency is common in adults with PWS (approximately 50%), and some would qualify for GH under current National Institute of Health and Care Excellence (NICE) guidance.[36]

DISCUSSION

An infant or child with PWS often has a large group of professionals and different developmental interventions involved in their care, and the requirements change with age (http://www.

pwsa.co.uk). The management and outcome of PWS has changed dramatically since it was first described in the 1960s. Severe disabling obesity in childhood has become the exception, and individuals with PWS are growing up slimmer and with fewer problems related to obesity. Factors in this improvement include early diagnosis, better information for families, clear dietetic and behavioural advice, improved developmental support services, and better management of complications. It is difficult to assess the added benefit from adding GH treatment to all these factors. Arguments against GH treatment in PWS include the burden of daily injections, the limited value of height gain for individuals with learning disabilities, the financial cost of the treatment, and the fact that you are not treating the most important problem in PWS, hyperphagia.

PWS is relatively rare and GH trials have all involved small numbers. There are controlled trials, but for most of these the period of study is relatively short, (the longest published is 7.9 years). We do not have studies looking at the benefit in treating throughout childhood, starting in infancy and continuing until early adult life, although this is now the treatment plan for many patients. International PWS groups support GH treatment as a standard for all children with the disorder, and it is unusual for a child with PWS in the developed world not to be treated with GH. Families and PWS groups are very positive about the contribution of GH treatment towards better long-term outcomes.

The NICE assessment of GH treatment in children calculated a cost of £7030 per cm height increment and cost per quality adjusted life year £115 755 in PWS; both costs are much greater than for any of the other conditions assessed, but were calculated only for the height increase with treatment.[37] NICE approval of GH for PWS was based on the acceptance that changes in body composition and reduction in cardiovascular risk were important factors. In PWS, the cost of GH treatment from infancy until adult height must be balanced against potential savings in developmental and medical care. The cost of medical and residential care for a severely obese young adult with multiple medical conditions for even a short period is greater than the cost of childhood GH treatment. A study of 12 individuals with PWS, aged over 50 years, found that the majority had several chronic health problems (foot problems 10/12, peripheral oedema 9/12, diabetes 6/12). They were taking multiple medications (1–13 with an average of 5.9 medications per individual). There were more individuals with severe intellectual disability in this group, and the authors speculate that these individuals are more likely to have lived in more structured residential environments, which prevented early obesity, although mean BMI at the time of the study was 31.5 kg/m^2 (range 23.4–37.1).[13] Long-term data are lacking, but if the benefits of GH treatment for PWS in childhood continue into adult life this would be likely to have an impact on long-term morbidity.

There is ongoing research into the basis of hyperphagia in PWS. This could lead to a targeted treatment, and if this happened, GH treatment in PWS might become obsolete. We have evidence to support the use of GH in children with PWS for body composition and developmental endpoints. More limited data supports starting in infancy, and logic suggests we should start before obesity occurs. Early treatment with GH, combined with strategies to control food intake and the food environment certainly has a role in improving outcome for children with PWS. Very long-term, randomised control studies are now unlikely to happen because GH is already accepted as standard care. Detailed follow-up of our current patients as they move into adult life is needed. The care of adults with PWS has many challenges, and the value of our paediatric care (including GH) is diminished if we do not have good transition to adult care for our patients. PWS is a good example of a condition where paediatricians need to be advocates for better services when patients leave their care.

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