Prader-Willi Syndrome

Chris Smith, RD, Senior Paediatric Dietitian,
Royal Alexandra Children's Hospital, Brighton, UK

Prader-Willi syndrome is a rare condition, with few specialist UK centres. The syndrome has many hallmarks, with hyperphagia (excessive eating) being the most well known characteristic associated with the condition. However, for a condition that is so intrinsically and chronically linked with food, many dietitians in the UK may never meet a patient with the condition or be involved in their management.

This article will cover the basics of paediatric dietetic management, including the assessment of nutritional status and different dietetic approaches, and explore the latest developments and progress in this area.

Introduction

Prader-Willi syndrome (PWS) is a rare genetic disorder in which genes on chromosome 15 are either deleted or unexpressed. Suspicion of diagnosis almost always arises from the clinical picture of infant hypotonia. This hypotonia impacts on all muscles, including the muscles for swallowing, which leads to poor feeding and, ultimately, poor growth.

Diagnosis is confirmed with genetic testing, which needs to be specifically requested, as PWS is not part of routine genetic testing. The three main molecular mechanisms that result in PWS are: paternal deletion, maternal uniparental disomy (UPD) and imprinting defect. On diagnosis, all families should receive genetic counselling. The prevalence of PWS in Europe has been reported between 1 in 8,000 to 1 in 45,000 births,[1] and in the US between 1 in 12,000 to 1 in 15,000.[2]

If weight is uncontrolled as the the child grows, co-morbidities can become common and can have a significant impact on life expectancy. However, if weight is well controlled, life expectancy may be normal.

No cure for the condition is presently available. Therefore, treatment centres on the careful management of symptoms, with diet and intake being pivotal to this.

Characteristics and phases

PWS is associated with multiple characteristics, but with variation in the severity of the involvement or impact of these. No phenotypic feature is known to correlate exclusively with any one of the three main molecular mechanisms. Characteristics include:

- Hypotonia
- Typical facial appearance
- Short stature
- Hypogonadism
- Varying degrees of developmental delay
- Scoliosis
- Sleep disturbances
- High pain threshold
- Speech apraxia/dyspraxia
- Infertility
- Poor/immature emotional and social development.

Historically PWS was associated with two distinct nutritional stages. Firstly, faltering growth in infancy and, secondly, hyperphagia with obesity in early childhood. More recently, an American group have clearly defined five detailed nutritional phases of PWS and described the characteristics of these – see Table One.[3]

Dietetic management

Control of weight and support of optimal growth is a key responsibility of the managing dietitian and multidisciplinary team (MDT), as the impact of weight can have wide-reaching consequences on many aspects of health and social development. Throughout the first 18 years different priorities and support are required. In practice, early management often takes the form of supporting growth, commonly through the use of nasogastric (NG) tube feeding, as consuming adequate feeding volumes is difficult. NG tubes remain in place for varying amounts of time, but are commonly no longer required by 18 months. For this reason, in practice, percutaneous endoscopic gastrostomy (PEG) tubes are not routinely placed as in nearly all cases the child's strength improves so they are able to self-feed successfully. Care must be taken to support gradual catch up with NG tube feeding to ensure recovery of early growth failure and, at the same time, not overshoot the proportional centiles. At this time, priorities switch to identifying and embedding a structured and controlled intake approach. As hyperphagia sets in, management focuses on balancing sufficient intake to support growth with careful avoidance of an excess of calories. The Prader-Willi Association UK (PWSA), in collaboration with the dietetic PWS Group, have developed dietary information for different age stages.[4]

Growth monitoring

Infant growth failure, early childhood obesity, absent pubertal growth spurt and adolescent short stature are common growth hallmarks of PWS children. These, coupled with inherent altered body composition,[5] make the interpretation of growth for PWS children difficult on standard UK growth charts.

In recent years, centile charts for non-growth hormone treated[6] and growth hormone treated[7] children have been published from a group in the US. Whilst these are not to replace standard growth charts, they are recommended to be used for evaluating growth for comparison purposes, monitoring growth patterns, nutritional assessment and recording responses to growth hormone therapy. They describe how PWS children grow but are not a descriptor of how they should grow. Therefore, an explanation of their use with families is necessary in order to prevent confusion.

Body composition is inherently different in people with PWS, with a lower lean body mass shown, even in very young infants and toddlers.[5] Body composition measurements for monitoring purposes may be useful, although care with interpretation is required, as no reference data specific to PWS exists at this time.

Nutrient intake – approach

Many dietary approaches have been described both in the literature and anecdotally. These include:

- Simple low calorie
- Low fat
- Vegan
- Single plate rule
- High protein, restricted carbohydrate
- Pyramid
- Raw diet
- Paleo
- Ketogenic.

Most recently, there has been a surge in interest and anecdotal use of the ketogenic diet for PWS. Although, there is a lack of any clinical data to support either its safety or its effectiveness in this condition. The concept of macronutrient proportion manipulation has been the subject of a clinical trial in the US, and the impact both on weight and body composition were favourable at 30% fat, 45% carbohydrates and 25% protein.[8]

It is difficult to conclude which, if any, of the many approaches that have been proposed is the most suitable for the condition and each patient should be considered individually. From experience, the consistency of the approach most likely plays a significant role. Advice for families when they are considering an approach is to ensure which they choose is specific, realistic, reproducible and safe.

Calories

Whilst the approach used by families to support growth and prevent rapid weight gain has some flexibility, the calories that are delivered have little room for manoeuvrability. Indeed, the tightrope walked of calorie balance is thin, where even a small increase may result in a significant weight gain. Controversy exists on the exact calorie requirements of PWS children, but the general agreed international principle is typically 60% of the recommended daily allowance (RDA).[9] Other approaches suggested include using height – 10-12 calories/cm of height for weight maintenance and 6-8 calories/cm of height for weight loss.[10] In practice, assessment and interpretation of growth patterns is essential to guide caloric increments up or down for weight control.

Balancing the provision of sufficient calories to support height/overall growth, with the avoidance of any excess calories, requires regular assessment and evaluation.

Micronutrients

Unlike calorie requirements, micronutrient requirements in PWS are thought to be the same as non PWS. This presents a challenge to dietitians in order to ensure all nutrients are met, despite having a significantly reduced calorie and portion intake. Just two studies[11, 12] have investigated the micronutrient intakes in PWS children. Whilst not completely in consensus, nutrients that have been shown to run low in a typical PWS diet include iron, vitamin D and calcium. To date, no studies of this patient group have included the assessment of zinc and selenium intakes. However, zinc and selenium have been shown to be two of the nutrients that were highlighted as very likely to be below the lower reference nutrient intake RNI (LRNI) in a UK pilot study.[13] The principle of focus on diet quality, as well as quantity, in this condition is vital.

Table One: Nutritional Phases of PWS

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

Source: Miller L, et al. (2011)[3]

Supplements

Supplementation with vitamins and minerals is internationally recommended in this group,[14] and screening for biochemical micronutrients can be considered if there are concerns.

Other supplements are not universally recommended and variance in practices and approaches exist. Most notably, carnitine and coenzyme Q10 are regularly prescribed for PWS patients in the US. These are not available on prescription in the UK, nor are they routinely recommended due to the lack of evidence. An investigation using serum sampling found no difference in levels in PWS patients compared with obese or sibling control groups.[15]

Behaviour management

Current literature recognises that eating behaviours in PWS are a complex phenomenon and they may involve a dysfunctional satiation rather than excessive hunger.[16] Wider behaviour traits commonly include:

- Preference for rigid routine
- Difficulty coping with change
- Difficulty coping with emotions
- Temper tantrums
- Stubbornness/oppositional behaviours
- Manipulative behaviours
- Obsessive-compulsive characteristics
- Psychosis (affecting 10%-20% by young adulthood – more frequent in those with UPD).

Understanding and appreciating these behaviours needs to be considered when managing the diet of a PWS child. Whilst many can be seen as barriers, several can act as an advantage to diet approaches, such as the preference for rigid schedules or routines. Others, such as a resistance to change, can make diet manipulation difficult. Offering food as a reward or withholding food as a punishment is almost always counterproductive. Food scavenging, ingestion of inappropriate foods (such as from bins) and stealing food can be common. Attitudes to locking cupboards and fridges vary between families but the principle of removing unsupervised access to food is essential. Regular evaluation of access should be recommended, and any periods of unexplained weight gain should lead professionals and families to consider or re-evaluate access.

The importance of food security and the understanding that disappointment surrounding food is a major source of behaviour problems should not be underestimated. A US group from Pittsburgh have championed an approach to address this entitled 'No doubt, no hope, no disappointment',[17] the principles are:

- No doubt about what food will be provided and when
- No hope of obtaining food outside the plan
- No disappointment concerning food as expectations have been managed.

In combination, all of these reduce the stress around food for the PWS patient. This is not necessarily a principle that can be applied for all PWS children, but it is an example of how diet strategies are closely linked with behavioural approaches.

Activity

Incorporation of activity into the daily life of PWS children should begin as early as possible in order to entrench this as a key part of lifestyle. Some activity for PWS children may be more physically difficult due to their lower muscle tone and increased tiredness, but identification of activity that is achievable and enjoyable is important. A small prospective study in pre-pubertal PWS children from the Netherlands showed daily muscle training increased lean body mass when compared to controls, although it did not normalise lean mass.[18]

Medical management

One of the cornerstones of medical management of PWS is the early use of growth hormone (GH) therapy. A systematic review and international guideline for the use of GH therapy in PWS was published in 2013.[19] Use of GH is agreed by the National Institute for Health and Care Excellence (NICE)[20] and is associated with many benefits, including:[21-24]

- Improving height growth
- Promote leaner body composition
- Increasing energy expenditure
- Improved weight management
- Increasing energy and physical activity
- Improving strength, agility and endurance
- Improving respiratory function.

The use of GH therapy necessitates the involvement of a specialist endocrinologist to monitor doses and impact.[19] Whilst it has many benefits, the importance and requirement for ongoing careful dietary management remains. Other medical management issues that need to be addressed include: hypogonadism, hypothyroidism, central adrenal insufficiency and bone health, including scoliosis.

No pharmaceutical treatments are available to treat or manage hyperphagia. Whilst surgical interventions, such as gastric bypass, have been used in adults with PWS, these are not recommended as treatments and are associated with high complication rates.[25]

Monitoring

Several UK MDT PWS clinics exist. Whilst there are no national or NICE guidelines in this area, the literature does describe the success of MDT approaches. Whilst there may be differences in clinic styles, the fundamental principles of care are much the same. Detailed monitoring guidelines have been published from the US.[26] These suggest evaluating diet (including adequacy of vitamin and mineral intake), growth parameters (height, weight, and BMI), and activity:

- Every month in infancy
- Every six months in the first decade of life
- At least annually thereafter.

A UK oversight document was developed with the PWSA to signpost and support monitoring practices.[27]

The future

Currently, PWS has no cure, but international work is continuing to explore potential treatments for PWS.

The drive to promote this is high. One such example is the Foundation for Prader-Willi Research which developed a global PWS registry in 2015.[28] One of the primary aims of this registry was to develop a comprehensive database of individuals with PWS to expedite the completion of clinical trials. The registry now has over 1000 patients who contribute, and it is being used to shape and prioritise areas of research and treatments.

Broadly, five main areas are being pursued:

- Genetic therapies
- Implanted devices (e.g. vagus nerve stimulation)
- Medications to impact behaviour (e.g. oxytocin)
- Medications to address hyperphagia (e.g. diazoxide choline controlled-release (DCCR))
- Use of cognitive therapies (e.g. cognitive behavioural therapy (CBT)).

Oxytocin is released by all mothers at birth and dynamically moderates the autonomic nervous system. Early oxytocin trials initially showed some very encouraging results in respect of behaviours in PWS children which drove an interest in this area.

Subsequent trials also showed some positive results. However, it should be cautioned that a recent comprehensive review in 2018 of all studies concluded that due to limitations, there is currently no convincing evidence that oxytocin improves symptoms.[29] Although, work continues in this area with a phase 2 randomised double-blind treatment trial of intranasal oxytocin, currently recruiting a target of 50 children in the US.[30]

DCCR is an ATP-dependent potassium channel agonist. In a phase II study, DCCR showed promise in addressing hyperphagia in PWS patients. In May 2018, a phase III clinical trial was announced. This is also currently recruiting in the US and will be a multi-centre, randomised, double-blind, placebo-controlled study including approximately 100 PWS patients.[31]

The application of CBT is increasing across a wide variety of conditions and PWS is no exception. Temper outbursts can be a regular situation faced by many families which can be disruptive and problematic. Subsequently, the need for an understanding in this area and practical strategies are of high importance for families. Dr K Woodcock has been leading this field in the UK and published data on this topic earlier this year, describing three themes within outbursts: goal blockage, social injustice, and difficulty dealing with change or task switching.[32] Dr Woodcock has developed a videogame prototype to improve individual's task switching and allow people with PWS to experience change with fewer temper outbursts. Dr Woodcock presented her most recent work at the PWA national conference in October this year.

The future of all of these directions of research remains uncertain. However, the drive to progress comes strongly from the international PWS community.

A UK-wide survey by the PWSA is currently underway.[33] This will provide a much needed, up-to-date, snapshot of UK services and what life is like for people living with PWS. We anticipate that the data from this survey will further help the development of national guidelines and help prioritise the needs for this group of patients.

In summary

PWS is a rare and complex condition. The pressures on the families and carers of this group are huge and the dietary challenges faced on a daily basis are a major part of this.

Whilst the pre-conceived picture of PWS historically is obesity, this should neither be seen as inevitable or irreversible. With careful planning, food security, and a consistent dietary approach, weight management and weight loss can be successful and be a source of achievement and pride for patients. Close MDT working with endocrine specialists, developmental paediatricians and clinical psychologists will further maximise the positive impact of dietetic involvement in this group.

Working in PWS is highly rewarding, as good quality nutritional support contributes significantly to PWS individuals achieving their full potential.

"Diagnosis is confirmed with genetic testing, which needs to be specifically requested, as PWS is not part of routine genetic testing."

References: **1.** Krasińska A, Skowrońska B (2017). Prader-Willi Syndrome nutritional management in children, adolescents and adults. Pediatr Endocrinol Diabetes Metab.; 23(2): 101-106. **2.** Bar C, et al. (2017). Early diagnosis and care is achieved but should be improved in infants with Prader-Willi syndrome. Orphanet J Rare Dis.; 12(1): 118. **3.** Miller JL, et al. (2011). Nutritional phases in Prader–Willi syndrome. Am J Med Genet.; 155A(5): 1040-1049. **4.** PWSA (1984). Accessed online: www.pwsa.co.uk/ **5.** Eiholzer U, Blum WF, Molinari L (1999). Body fat determined by skinfold measurements is elevated despite underweight in infants with Prader-Labhart-Willi syndrome. J Pediatr.; 134(2): 222-225. **6.** Butler MG, et al. (2015). Growth charts for non-growth hormone treated Prader-Willi syndrome. Pediatrics; 135(1): 126-135. **7.** Butler MG, et al. (2016). Growth Charts for Prader-Willi Syndrome During Growth Hormone Treatment. Clin Pediatr (Phila).; 55(10): 957-974 **8.** Miller JL, et al. (2013). A reduced-energy intake, well-balanced diet improves weight control in children with Prader–Willi syndrome. J Hum Nutr Diet.; 26(1): 2-9. **9.** Driscoll DJ, et al. (1998). Prader-Willi Syndrome. In: GeneReviews®. Accessed online: www.ncbi.nlm.nih.gov/books/NBK1330/ (Nov 2018). **10.** Butler M, Lee P, Whitman B (Eds.) (2006). Management of Prader Willi syndrome. Third edition Springer. New York. P23. **11.** Lindmark M, et al. (2010). Nutrient intake of young children with Prader–Willi syndrome. Food Nutr Res.; 54: 10.3402/fnrv54i0.2112. **12.** Rubin DA, et al. (2015). Nutritional intakes in children with Prader-Willi syndrome and non-congenital obesity. Food Nutr Res.; 59: 10.3402/fnrv59.29427. **13.** Smith C, et al. (2017). G152 Micro-nutrient intakes in calorie restricted diets of children with prader-willi syndrome. Arch Dis Child.; 102: A62-A63. **14.** Butler MG, Hanchett JM, Thompson T (2006). Clinical findings and natural history of PWS. In: Management of Prader-Willi Syndrome. 3rd edition. New York: Springer-Verlag; 23-24. **15.** Miller JL, et al. (2011). Carnitine and coenzyme Q10 levels in individuals with Prader-Willi syndrome. Am J Med Genet A.; 155A(3): 569-573 **16.** Martínez Michel L, Haqq AM, Wismer WV (2016). A review of chemosensory perceptions, food preferences and food-related behaviours in subjects with Prader-Willi Syndrome. Appetite; 99: 17-24. **17.** Gourash LM, Forster JL (2009). Developmental and Behavioral Pediatrics Developmental NeuropsychiatryPrader-Willi Syndrome: The Behavioural Challenge. A brief summary for professionals. Pittsburgh Partnership. Accessed online: http://pittsburghpartnership.com/handouts/The%20Behavioral%20 Challenge%20for%20Professionals.pdf (Nov 2018). **18.** Schlumpf M, et al. (2006). A daily comprehensive muscle training programme increases lean mass and spontaneous activity in children with Prader-Willi syndrome after 6 months. J Pediatr Endocrinol Metab.; 19(1): 65-74. **19.** Deal CL, et al.; 2011 GH in PWS Clinical Care Guidelines Workshop Participants (2013). GrowthHormone Research Society Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome. J Clin Endocrinol Metab.; 98(6): E1072-1087. **20.** National Institute for Health and Care Excellence (NICE) (2010). Human growth hormone (somatropin) for the treatment of growth failure in children. Technology appraisal guidance. Accessed online: www.nice.org.uk/guidance/ta188/resources/human-growth-hormone-somatropin-for-the-treatment-of-growth-failure-in-children-pdf-82598502860485 (Nov 2018). **21.** Lindgren AC, et al. (1998). Growth hormone treatment of children with Prader–Willi syndrome affects linear growth and body composition favourably. Acta Paediatr.; 87: 28-31. **22.** Carrel AL, et al. (1999). Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader–Willi syndrome: a controlled study. J Pediatr.; 134(2): 215-221. **23.** Davies PSW, et al. (1998). Effect of growth hormone on height, weight and body composition in children with Prader–Willi syndrome. Arch Dis Child; 78(5): 474-476. **24.** Siemensma EP, et al. (2012). Beneficial effects of growth hormone treatment on cognition in children with Prader–Willi syndrome: a randomized controlled trial and longitudinal study. J Clin Endocrinol Metab.; 97(7): 2307-2314. **25.** Scheimann AO, et al. (2008). Critical analysis of bariatric procedures in Prader-Willi syndrome. J Pediatr Gastroenterol Nutr.; 46(1): 80-83. **26.** McCandless SE, and The Committee on Genetics (2011). Clinical Report – Health Supervision for Children with Prader-Willi Syndrome. Pediatrics.; 127(1): 195-204. **27.** PWSA (2017). Prader-Willi Syndrome (PWS): Multi-Disciplinary Paediatric Health Oversight. Accessed online: www.pwsa.co.uk/ PWS_Multi-Disciplinary_FINAL_web_version.pdf (Nov 2018). **28.** FPWR (2018). Global PWS Registry. Accessed online: www.fpwr.org/global-pws-registry (Nov 2018). **29.** Rice LJ, et al. (2018). A review of clinical trials of oxytocin in Prader-Willi syndrome. Curr Opin Psychiatry.; 31(2): 123-127. **30.** Foundation for Prader-Willi Research (FPWR) (2018). Intranasal Oxytocin vs. Placebo for the Treatment of Hyperphagia in PWS. Accessed online: www.fpwr.org/clinical-trials/in-oxt-study **31.** FPWR (2018). DCCR for the Treatment of Hyperphagia in PWS. Accessed online www.fpwr.org/clinical-trials/dccr (Nov 2018). **32.** Rice LJ, et al. (2018). The characteristics of temper outbursts in Prader-Willi syndrome. Am J Med Genet A.; doi: 10.1002/ ajmg.a.40480 [Epub ahead of print]. **33.** PWSA (2018). PWSA UK Surveys Open. Accessed online: www.pwsa.co.uk/news-page/pwsa-uk-surveys-open (Nov 2018).