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Review

A short clinical overview of Prader–Willi syndrome

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Summary

Prader–Willi syndrome (PWS) is a multifaceted developmental disorder most commonly associated with extreme hyperphagia and life-threatening obesity. PWS is a genetic disorder of imprinting with almost all cases occurring spontaneously. Behavioural and imaging studies have shown that obesity in PWS arises from overeating driven by a faulty satiety mechanism which manifests as an almost permanent state similar to starvation. With no available treatments, management of the eating behaviour is the only option and has two main strategies: restrict access to food and distract thoughts from food. In this mini review, which we have aimed at clinicians, we outline the main aspects of PWS including genetics, development of the eating behaviour and best practice approaches to management.

Keywords: hyperphagia, management, Prader–Willi Syndrome.

Introduction

Prader–Willi syndrome (PWS) was first described in 1956 by three Swiss endocrinologists as having the characteristics H3O: hypotonia, hypogonadism, hyperphagia and obesity (1). As well as these core features, PWS affects many systems and can also result in infantile failure to thrive, hypopigmentation, facial features including almond-shaped eyes, psychiatric issues, short stature, scoliosis and intellectual disability (ID). It is also associated with behavioural issues, temper tantrums, skin picking and autistic features. PWS currently affects around 1 in 22–25 000 live births (2–4) and is associated with morbidity that is six times higher than that of other IDs (5). Typically, PWS is considered as a disorder of insatiable appetite and unavoidable obesity. In reality, however, the behavioural picture is more complex and varies considerably from person to person. In this review, we outline the main issues that clinicians dealing with PWS must be familiar with, from genetics to management.

Genetics of Prader–Willi syndrome

It is now known that PWS is an imprinting disorder and is caused by absence of paternal contribution at the Prader–Willi/Angelman critical region (PWACR) on chromosome 15, although the exact gene/s responsible remains unclear. Specifically, advances in genetics in the late 1980s demonstrated that PWS is caused by the lack of expression of maternally imprinted/paternally expressed genes in the region q11-q13 of the paternally inherited chromosome 15 (6). A lack of maternal contribution at PWACR results in the clinically distinct Angelman's syndrome. There are two main genetic mechanisms resulting in PWS. The most common genetic error, accounting for around 70% of people with PWS, is a deletion in the critical region. The second most common error, maternal uniparental disomy (mUPD), accounts for around 25% of people with PWS and is caused by inheritance of two maternally derived, but no paternally derived, chromosome 15s. Genes that are imprinted depending on the gender of the parent of origin are expressed only from one chromosome, being 'switched off' on the other analogous chromosome. Thus, maternally imprinted genes are expressed only from the paternally derived chromosome, and paternally imprinted genes are expressed only from the maternally derived chromosome. It is not known how many imprinted genes there are in the critical region or the absence of how many of them contribute to the syndrome. It is to be noted that non-imprinted ('normal') genes can be expressed from

either the maternally derived or the paternally derived chromosome, and hence expression of non-imprinted genes is not lost in PWS. PWS can also be caused by imprinting defects and imprinting centre mutations, although this is much rarer than deletion and mUPD.

The genetic subtype of PWS appears to some extent to influence the resulting phenotype. For example, PWS of deletion type tends to result in typical PWS facial features, increased tendency to skin picking (7) and lowered risk of psychiatric problems (8–11) compared to mUPD. The deletion subtype can be further split into two groups depending on the size of the deleted segment: Type I, which results from a chromosomal break at break point 1; and Type II, which results from a break at point 2, and results in a smaller deletion than Type I. There are suggestions that people with Type I deletion show poorer adaptive behaviours, academic performance and poorer social skills compared to Type II, see (12). Compared with deletion, mUPD is associated with older maternal age (13,14) which may explain the increase of mUPD-related PWS as average maternal age increases in the general population (15).

Genetic testing is mandatory to diagnosis. DNA methylation analysis is the only technique that can both confirm and reject the diagnosis of PWS and is therefore the first choice for investigation, although it cannot determine genetic subtypes, see (16,17). During childhood a genetic test should be considered in all obese children with ID (16). Clinicians should be aware that people now in their twenties or older may have never been genetically tested. In fact, as we have seen in our research group, there are people who may have been wrongly diagnosed with PWS in infanthood.

Phenotype of Prader–Willi syndrome

The phenotype of PWS is evident early on and may begin *in utero* (18). Women with PWS babies experience more pre- and perinatal complications than normal (19,20). At birth, the baby with PWS is of normal length but tends to be underweight (19,20) and is observed to be severely hypotonic. Hypotonia is such a core symptom of PWS that it is recommended that all hypotonic babies should be tested for PWS (21). In striking contrast to the later phenotype, almost all PWS infants have poor suck and difficulty feeding. Most PWS babies are tube fed and prefer to sleep rather than feed, which accounts for a drop in weight following birth (22). This assisted feeding stage lasts an average of 9 months (14). The baby also has very small or hypoplastic genitalia and almost all male babies have undescended testes. The hypotonia gradually diminishes over time, but in a significant number walking is delayed and activity levels remain low in most. Height increases more slowly than normal because of very low growth hormone (GH) levels, but after a slow start weight increases more rapidly than normal (22). There is increasing evidence that the acceleration in weight gain begins before the child shows an increased interest and intake in food consumption, perhaps with a stage of normalized feeding behaviour relative to peers (14,16,22,23). During this stage, it is suggested that parents reduce calorie intake to 50–80% of the recommended daily allowance for the child (14).

In later childhood, what was once considered the 'second phenotype' of PWS develops. The inevitable excessive interest in food that emerges is very variable in children and may initially manifest as an obsessive interest in recipe books, specific play behaviours, food as a topic of conversation, stealing food or by active foraging in cupboards and sometimes bins. When combined with the effects of residual low muscle tone, the developing obesity results in a further decrease in physical activity which in turn further exacerbates the weight increase. In experimental settings, people with PWS are reported to eat far greater than the normal calorific intake, consuming 1292 calories compared to 369 calories in lean controls in 1 h (24). In as-yet unpublished research studies in our group, some individuals with PWS will consume up to 3200 calories during an hour's free access to food. The later childhood phenotype is also characterized by mild to moderate intellectual disabilities, reduced hypotonia, hypogonadism, small stature and behavioural difficulties, especially repetitive and ritualistic behaviours (25). These characteristics seem to be universal in children and adults with PWS, although it is important to note that they vary in severity from person to person. A range of other characteristics have been described including sleep problems, of which excessive daytime sleepiness is the most common (26). Staying awake as a passenger in a car is particularly difficult. It is notable that many of these characteristics of the PWS phenotype have in common a deficiency of regulatory mechanisms which have been ascribed to a disorder of the hypothalamus (27). In addition, inability to vomit, skin picking and lowered sensitivity to temperature and pain are all more prevalent in PWS than in the general population but are not inevitable. In the earlier literature, these characteristics were described as present or absent in a given individual but, in view of their varying severity in the PWS population, are perhaps more appropriately conceived as having a distribution in PWS that is shifted towards the more severe extreme relative to their distribution in the general population. Maximal weight is usually reached in late adolescence, coinciding with transitions from school and from child to adult services. It is reported that in some cases, adults with PWS can 'grow out of' the eating phenotype, achieving feelings of satiety and being better able to control their food intake (14). More research into this stage is required.

Cause of obesity in Prader–Willi syndrome

Undoubtedly, beyond infanthood, the most distinguishing feature of PWS is the eating disorder. The view that abnormal feelings of hunger are driving the urge to eat has been largely discounted, and it is now generally agreed that the disorder arises from defective satiety mechanisms (24,28). A number of researchers have confirmed this with imaging studies by comparing brain regions activated by various stimuli when fasted and brain regions activated following various-sized meals both in controls and PWS. In the earliest report, fasted subjects were given a glucose drink while in the scanner, and time to activation of known satiety regions (insula, ventromedial prefrontal cortex, nucleus accumbens) was measured showing a distinct lag in response time in PWS subjects (29). A similar neural representation of hunger (fasting) was found in PWS and non-PWS participants, but the normal representation of satiety (i.e. that observed in the control group) was not found in the PWS group, even after a triple food load (30). The role of food preferences was also studied by Hinton and colleagues via pictures of previously-ascertained high- and low-preference foods tailored to each individual, and food preferences were not reflected in brain activation (31). It is likely that insensitive satiety is exacerbated by other atypical mechanisms, including hyper-responsive reward pathways. In a scanning study of responsiveness, pictures of food, animals and blurred images were shown before and after a meal to PWS and healthy-weight control participants. Greater activation to food pictures in food motivation brain networks was shown before the meal in the control group but after the meal in the PWS group (32). In another brain scan study, food pictures were found to enhance activation of reward centres, suggesting a motivation for increased food consumption (33). A further report found that this was particularly true of high calorie foods compared to lower calorie foods (34). A hyper-responsive reward system in response to food suggests that it may be helpful to consider food as a substance of misuse or abuse in PWS (35) [see (36) for review]. This may prove to be a helpful framework in considering management, especially the importance of avoiding food cues, to which people with PWS are sensitive (37).

Management of Prader–Willi syndrome

Overcoming physiological drives to consume that extra bit of cake is a struggle for almost all of us, and for individuals with PWS, relying on cognitive controls to resist food can require almost superhuman strength. To date, appetite-reducing drugs have proved ineffectual (38,39), and bariatric surgery is associated with high rates of mortality (40). Therefore, the only route in PWS is management, and planning with supervision and support keys factors in helping people overcome the eating behaviour. On reaching adulthood, a small minority of people with PWS allow their parents to continue to control their food intake, and a few voluntarily enter supported living environments where food access is strictly controlled (in the UK this is often Gretton Homes, residential care facilities specifically for people with PWS); it is important to note that in considering residential care, the best scenario is one in which all residents have restricted food access. Other adults with PWS may indulge their craving for food by rejecting advice and ignoring any supervisory structures that may be in place. This last group of people with PWS tends to become seriously obese, developing associated complications such as diabetes mellitus, high blood pressure, cellulitis, leg oedema and ulcers (41).

Common themes in studies of best management and in parental anecdotes

The key factors that should be reinforced in any plan of care for PWS are:

Early diagnosis

In a study with children diagnosed before the second month compared to those diagnosed at average age of 36 months, early diagnosis of PWS combined with multidisciplinary care was shown to reduce hospitalization time, reduce duration of tube feeding and prevent early obesity in PWS infants (42).

Multidisciplinary teams

For best care, teams should include, among others, endocrinology, psychiatry, psychology, dieticians, orthopaedics and speech therapy depending on individual needs (16). In the case of severe obesity, cardiologists and pulmonologists should also be involved (17).

Early introduction of growth hormone

GH has been shown to improve body composition in PWS (43,44). When started in infancy, GH improves body fat levels, and muscle strength (45), meaning that some people will be able to avoid the obesity that was once so characteristic of the syndrome. It should be noted, however, that there have been concerns with unexpected deaths in children undergoing GH treatment, and treatment should be considered carefully.

Exercise and diet

Routine daily physical activity of at least 30 min is strongly recommended (46). Lower calorie intake is required

because of low muscle tone, and 'tricks' such as using smaller plate sizes can help people to eat less.

Removal of food-related stresses

For people with PWS, it is often noted that behavioural outbursts and anxieties can be reduced when the individual knows when the next meal is coming, what it will comprise, and how much they will be allowed. Gourash and Forster of The Pittsburgh Partnership have encapsulated this in 'Food Security' which denotes the principles of 'no doubt', 'no hope' and 'no disappointment' in relation to the individual's capacity for self-regulation with respect to meals. Individuals with PWS are known to like routine (47) and are often upset with change, for example, many with PWS would be very distressed if they were presented with an unexpected situation.

Liaison with schools

Difficulty with schooling, particularly within mainstream schools, is a common theme throughout parental and clinician anecdotes. This is possibly affected by the fact that people with PWS have deficits with social cognition (48). Families and clinicians should make schools aware that PWS is a complex disorder affecting many faculties, and that teachers should be aware of the importance of limited access to food, the difficulties children face with physical education in respect to their low muscle tone and the potential for behavioural outbursts.

Distraction from food

Distracting people with PWS from food is a coping strategy for many parents. This can include engaging the person with chores or puzzles.

Do not use food as a reward

GP surgeries, dentists and teachers should be aware that rewarding PWS children with food for good behaviour should never be an option.

Conclusion

In this mini review, we have outlined the main factors of PWS that obesity clinicians should be aware of. In particular, our review shows that (i) obesity is not due to a 'lack of will-power'; (ii) that 'counselling' the person with PWS will not help; and (iii) that parents should not be expected to take full responsibility – some can cope but not all. Despite many advances in research of PWS, access to clinical services is still limited and people with IDs and obesity are subject to health inequalities (49). Transition to adult services can be particularly troublesome as it is often not clear what services children should go to (for example, ID services), and this conversion should be planned for as much as is possible. Support for families should also be a consideration, with 70% of PWS mothers needing counselling for stress (50). More information for families is available from organizations such as the PWS Association UK. Despite a lack of the all-important cure for hyperphagia, earlier diagnosis combined with multidisciplinary approaches to management means that the younger PWS generation has a more positive prognosis than the previous one.

Conflict of Interest Statement

The authors declare no conflict of interest.

Author contributions

Both authors were involved in writing the manuscript and had final approval of the final version.

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