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Prader-Willi syndrome

Care of adults in general practice

Background

Prader-Willi syndrome is a severely disabling genetic condition. Treatments are available, but there is no cure. Children aged up to 18 years may benefit from growth hormone treatment, which normalises height and assists in preventing obesity by decreasing fat mass and increasing muscle mass and physical ability. Adults, however, are treated predominantly for the many disabling secondary complications of the morbid obesity characteristic of this syndrome, and therefore require frequent care from their general practitioner.

Objective

Despite improvements in the genetic diagnosis of infants with Prader-Willi syndrome, diagnosis in adults appears to be lacking or is based on uncertain clinical characteristics. This article provides information and advice that may assist in the diagnosis and management of Prader-Willi syndrome in adults.

Discussion

The GP can play an important role in identifying Prader-Willi syndrome among adult patients who may have remained undiagnosed. Specific care and treatments can then be provided in the general practice setting.

Keywords

Prader-Willi syndrome; obesity; endocrine system diseases; growth hormone

Prader-Willi syndrome (PWS) is characterised by short stature, small hands and feet, an abnormal body composition (reduced lean tissue and increased fat mass), developmental delay, mild to moderate intellectual disability, characteristic behaviours and psychological problems.[1,2] Low levels of growth hormone and sex hormones are common,[3,4] and thyroid function may be impaired.[5] A hypothalamic dysfunction has been implied.[6]

Infants with PWS are floppy and inactive, have a weak cry, a poor suck and feeding problems, which lead to growth failure. This is followed by several characteristic stages in which feeding problems diminish, weight rapidly increases and hyperphagia develops at 1–4 years of age.[7,8] The pubertal growth spurt is generally absent and hence, short stature will be pronounced in adulthood.[9] Scoliosis and kyphosis are common and may be severe.[10] Hyperphagia, low muscle tone, respiratory and sleep problems, including excessive daytime sleepiness and lack of energy, exacerbate the tendency to become morbidly obese in the adolescent years, which is the major cause of mortality in adults with PWS.[2,11]

Growth hormone treatment

Subsidised growth hormone (GH) treatment has been approved by the Pharmaceutical Benefits Scheme for children with genetically confirmed PWS until the age of 18 years.[12] Growth hormone treatment normalises height in children and improves body composition by reducing fat and increasing lean tissue mass in children and adults with PWS.[13,14] The increase in muscle mass improves strength, tone and stamina for physical activity, which assists in weight management (*Figure 1*).[15] Improvement in bone density with GH treatment may prevent the onset of osteoporosis, which commonly develops in adolescents and adults with PWS.[16] The application for GH must be made by a paediatrician or endocrinologist and is only available on private prescription for adults. A preliminary sleep evaluation is obligatory if GH treatment is considered so that any existing respiratory problems can be addressed.

Incidence, prevalence and mortality

Information on the prevalence and mortality of people with PWS is limited. Mortality is high, approximately 3% per annum,[17] and the average age of death was 33.2 years in a study of adults.[18] In a recent Victorian study, however, the probability of survival was 94% until 20 years of age, but then declined rapidly, especially for those who are obese.[11]

The number of people in Australia with known PWS by year of birth, based on data from the Australian Prader-Willi syndrome database, is presented in *Figure 2*. At least 261 cases have been genetically confirmed and are seen in

hospital-based PWS clinics. One in 17 000 would be a conservative estimate of the birth incidence in the past two decades. Another 79, mainly older individuals with PWS are known to the Prader-Willi Syndrome Association of Australia. Information on adults diagnosed with PWS is scarce and the total number of adult patients seen by specialists or general practitioners is currently unknown. Diagnosis of adults may be based on clinical characteristics only, which are not always confirmed genetically.

Figure 1. Two adolescent girls with Prader-Willi syndrome. One (left) received growth hormone treatment for 4 years; the other (right) received no growth hormone treatment

Genetic diagnosis

The diagnosis of PWS has improved dramatically since 1989 when genetic testing for the various subtypes of the condition became available. These tests detect lack of expression of paternally contributed genes on chromosome 15q11–q13 due to deletion or maternal uniparental disomy.[19] DNA methylation analysis has a high reliability and specificity to test for all subtypes of PWS in contrast to previous diagnostic strategies, which relied on either clinical characteristics or chromosome studies.[2]

Diagnosis of children with PWS

Early diagnosis of PWS is important,[20] as late diagnosis may result in heightened behavioural problems.[21] Especially over the past decade, diagnosis of infants has improved their quality of life by multidisciplinary health management focusing on early intervention.[22] All infants with characteristic signs of PWS, as described in *Table 1*, should be referred for genetic testing.[23,24] Referral to a paediatric multidisciplinary PWS clinic is recommended for additional care. These are available in most capital cities in Australia.

Diagnosis of adults with PWS

Each year new diagnoses of PWS are made in patients aged in their 20s and 30s. Many people in this group seem to have previously been given an alternative diagnosis,[20] commonly general intellectual disability, Asperger syndrome, autism spectrum disorder or even some other chromosomal abnormality, such as a PWS-like subtype of Fragile X syndrome.

The GP or allied health professional can play a major role in identifying adults with PWS by re-assessment of an existing clinical diagnosis. For example, if an adult patient is short, obese, has intellectual disability or learning difficulties, and also has hypogonadism, small hands and feet, insatiable appetite and thick, viscous saliva (*Table 1*), a re-investigation for PWS is warranted.[20,23] In addition, a history of general feeding problems in early infancy that may have required tube feeding can often be considered confirmation of a clinical diagnosis of PWS (*Table 1*). Speech and articulation problems as well as skin picking are other highly characteristic features of PWS.[24]

Conversely, adult patients with a clinical diagnosis of PWS who do not have the characteristic features of hypogonadism and small hands and feet, mentioned in section 2 of *Table 1*, are likely to fail genetic confirmation of PWS.[23] Indeed, 10 out of 56 individuals diagnosed with PWS from disability services records failed genetic confirmation in a Western Australian study.[25]

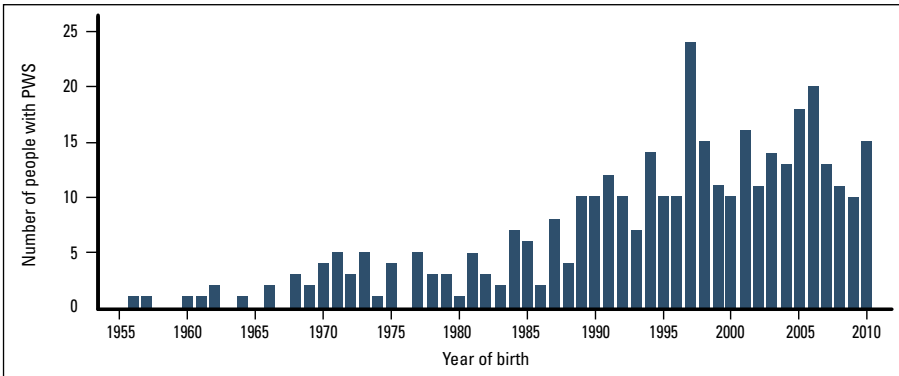

Figure 2. Number of people with Prader-Willi syndrome by year of birth in Australia since 1955
Data from the Australian Prader-Willi syndrome database and the Prader-Willi Syndrome Association of Australia

Management in general practice

While PWS is not common, patients with PWS visit their GP frequently due to the numerous chronic and sometimes acute problems related to obesity, respiratory function, sleep and behaviour. In addition, there are incidents such as choking, falls and injuries due to poor tone, coordination or intellectual disability. Patients with PWS are often hospitalised or need referral to specialist care. *Table 2* provides an overview of common problems encountered or followed up in general practice.[20,26–28]

Caution in interpretation of seemingly minor complaints in PWS

Often the severity of a clinical symptom may be underestimated until the condition warrants immediate attention. The following advice is specific to patients with genetically proven PWS.[29]

High pain threshold

Minor fractures or injuries are difficult to diagnose when there are few or no complaints of pain. Often it may be some days before a problem is suspected (eg. when a bruise or swelling doesn't disappear). A referral for an X-ray is advised whenever a fall has preceded a minor complaint of a sore limb.

Table 1. Presenting signs and symptoms suggesting referral for genetic testing for Prader-Willi syndrome

Infants	• Hypotonia • Poor suck or feeding problems • Weak cry • Inactivity Plus • Hypogonadism
Adults	• Short stature • Obesity • Mild to moderate intellectual disability Plus • Hypogonadism • Hyperphagia • Small hands and feet • Thick, viscous saliva Plus/minus • History of hypotonia, poor suck, general feeding problems in infancy

Table 2. Problems in Prader-Willi syndrome commonly encountered in general practice[23,26–29]

System	Common problems
Respiratory	Snoring Sleep apnoea and hypopnoea Excessive daytime sleepiness Infections (eg. pneumonia) Asthma
Endocrine	Type 2 diabetes mellitis Hypothyroidism
Cardiovascular	Hypertension Chronic leg oedema
Gastrointestinal	Constipation Reflux Inguinal hernia
Musculoskeletal	Fractures Dislocations Tendon tears Heavy bruising Osteoporosis
Dermatological	Infection due to trauma from skin picking Erysipelas
Psychological	Behavioural issues Psychosis Sexuality/abuse Difficulties with self-care/hygiene

Thermoregulation problems – lack of fever

Patients with PWS may not develop any fever, despite having a serious infection. Patients with PWS are especially prone to respiratory infections such as pneumonia. Undiagnosed, this can lead to death. On the other hand, 'sudden excessive fever' also occurs and may lead to fits. Both hyper- and hypo-thermia may occur in extreme weather conditions due to problems in thermoregulation.

Stomach problems

Overeating may lead to overextension and even rupture of the stomach. Due to high pain tolerance and difficulty in localising pain, the patient may just feel generally unwell. A referral to an emergency department is essential if the person complains of general abdominal pain and a bloating of the abdomen, especially if binge eating may have occurred and the person is not obese. An X-ray or CT scan should be taken or, in cases of serious pain or fever, an ultrasound or endoscopy should be performed as acute gastric dilation, inflammation, gastroparesis and necrosis are all more common in PWS than in the general population.

Lack of vomiting

People with PWS rarely vomit. This may be a concern, for example, if uncooked, spoiled or raw pet food has been eaten or non-food items have been ingested. Treatment for food poisoning or intoxication, for example from medication, is advised. Emetics are generally ineffective and their use is not recommended. Pumping the stomach and the use of activated medical charcoal are advised. On the other hand, if vomiting does occur in a patient who rarely, if ever, vomits, this may be a sign of a very serious or life-threatening problem.

Adverse reactions to medication or anaesthesia

Unusual reactions to standard dosages of medications or prolonged responses to sedation have been recorded.

Key points

- Prader-Willi syndrome is a severely disabling genetic condition of short stature and obesity.

- Growth hormone treatment has been endorsed to improve height and body composition of people with genetically confirmed PWS until the age of 18 years.
- Complications of obesity are a major cause of morbidity and early death in adults with PWS.
- A diagnosis of PWS in adults is often missed. In addition, diagnosis of PWS on only clinical characteristics is uncertain.
- A high pain threshold, absence of fever or vomiting, adverse reactions to medication or anaesthesia are specific concerns in patients with confirmed PWS, therefore genetic diagnosis is important.

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