Prader-Willi Syndrome (PWS)

First description

Prader-Willi syndrome (PWS) was first described in 1956 by Prader, Labhart and Willi. It was known as H3O syndrome because of the characteristic symptoms of hypotonia, hypogonadism, hyperphagia and obesity.

Genetics and molecular biology

PWS results from the absence of expression of the paternal allele of paternally expressed/maternally imprinted genes at the chromosomal locus 15q11-q13 (the PWS critical region). The commonest genetic mechanisms leading to PWS are: a) a de novo deletion at the PWS critical region on the chromosome of paternal origin (60%) and b) maternal uniparental disomy (mUPD) of chromosome 15 where both chromosomes are derived from the mother (36%) (Butler et al. 2019). Other rarer causes of PWS include imprinting centre defects (4%) and unbalanced translocations. A number of paternally expressed/maternally imprinted genes have been identified within the PWSCR of which the largest is SNRPN (containing the imprinting centre) which codes for a small nuclear ribosomal protein involved in the control of synthesis of proteins related to hypothalamic function. Imprinted and non-imprinted genes are found within the deleted region; SNORD 116, MAGEL 2 and NECDIN being the genes whose absence of expression at the locus 15q11-13 are considered central to PWS. Knock-out mouse models and studies of people with mutations in the MAGEL2 (i.e. Schaaf-Yang syndrome) and/or NECDIN genes suggest that these genes are involved in hypotonia, respiratory problems, sleep abnormalities, adiposity, developmental and cognitive delay, socialisation difficulties and skin picking (Fountain et al. 2017a, 2017b; Matarazzo et al. 2017; Muscatelli et al. 2000). However, two people have been described lacking expression of the genes MKRN3, MAGEL2 and NECDIN but showing only developmental and cognitive delay from the major PWS criteria (see Holm et al 1993 for consensus diagnostic criteria) and a high pain threshold from minor criteria (Kanber et al.2009; Buiting et al. 2014). Also, accounts in the literature of people with very small deletions, not involving MKRN3, MAGEL2 or NECDIN, but with most or all PWS characteristics also support the non-involvement of these genes in the PWS core characteristics in humans (Sahoo et al 2008; de Smith et al 2009; Duker et al 2010). Core characteristics in these cases were: hypotonia, early feeding difficulties, hyperphagia/obesity, hypogonadism, intellectual disability and behaviour problems. The most likely single candidate gene, from studies of people with PWS, is now considered to be the imprinted gene SNORD116. SNORD116 changes the expression levels of multiple genes (Falaleeva et al. 2015), which may explain why, in PWS, it is able to affect so many systems.

In developed countries, diagnosis is usually made clinically based on severe hypotonia at birth, and followed by genetic testing. Mahmoud et al. (2019) carried out a feasibility study which showed that newborn screening was accurate, able to differentiate genetic subtypes, and could lead to earlier intervention with better outcomes.

Incidence/prevalence

The estimated birth incidence is 1 in 25,000 (Whittington et al., 2001; Vogels et al., 2003; Smith et al., 2003; Diene et al., 2010). Prevalence will vary across populations and time according to the death rates: the higher the death rate, the lower the prevalence.

Natural history

The early phenotype is characterised by severe hypotonia after birth, which affects the infant's ability to suck, resulting in feeding problems and consequent failure to thrive which may necessitate gavage feeding. Hypothalamic dysfunction leading to growth hormone and steroidal sex hormone deficiency may account for several features of PWS (Goldstone 2004), including the control of birth processes, short stature, hypogonadism, aberrant body temperature control and daytime hypersomnolence. Characteristic facial features include dolichocephaly, narrow bifrontal diameter, almond shaped palpebral fissures, small down turned mouth and thin upper lip (Holm et al. 1993).

The onset of the striking characteristic of hyperphagia separates the early and late phenotype. Between the ages of 1 and 6 years, the child develops a propensity for eating which, if left unaddressed, can result in obesity and medical problems. The hyperphagia is considered to be hypothalamic in origin, and caused by failure of the normal satiety response following food intake (Holland et al. 1993; Hinton et al. 2005). Infertility remains almost universally present although there are rare reports of children being born to females with PWS.

Behavioural and psychiatric characteristics

The main behavioural techniques used to address hyperphagia include preventing access to food e.g. by locking cupboards, low calorie diets, all members of the household having the same diet and ongoing education about the risks of overeating. Appetite suppressants and gastric banding have not been shown to be useful. Octreotide has been shown to decrease concentrations of ghrelin in adolescents with PWS, but does not reduce appetite or BMI (De Waele et al. 2008). This year the drug Vykat XR has been approved in the USA (2025) for treatment of hyperphagia in PWS.

Aside from the over-eating, the most common problem behaviours are temper tantrums, mood swings which do not fulfil criteria for a defined psychiatric disorder; ritualistic and repetitive behaviours; and self-mutilation in the form of skin-picking. Evidence suggests that modulation of the glutaminergic pathway may reduce the compulsive behaviours; oral N-acetylcysteine was found to reduce skin picking, although participants with PWS were not compared with a control group (Miller & Angulo 2013). A small study of vagus nerve stimulation found great improvement of problem behaviours, although not hyperphagia (Manning et al. 2016)
A comprehensive study of 101 participants with PWS found that temper outbursts decreased in frequency with age, while the duration of outbursts increased. Provocations fitted in to three themes: goal blockage, social injustice, and difficulty dealing with change. Medications were prescribed, but were not found to be particularly effective (Rice et al. 2018).Temper outbursts are associated with task switching and can be reduced by signalling in advance that a change is coming (Bull et al. 2017)

Relative to others with intellectual disability, people with PWS are more likely to exhibit severe problem behaviours (Dykens et al. 1997). Obsessional traits occur commonly, in particular needing to ask or tell, requiring routines, hoarding and repetitive questioning (Clarke et al. 2002). It has been found that people with PWS who are exposed to routines for longer before a change are more likely to engage in temper outburst behaviours (Bull et al. 2014).

The mUPD genetic subtype of PWS is strongly associated with the development of affective psychosis (Boer et al 2002). In a UK-wide sample of 119 adults with PWS, 62% of those with mUPD had a diagnosis of psychotic illness compared with 17% of those with a deletion (Soni et al. 2008). Atypical symptoms such as hypersomnia and confusion were seen, and those with mUPD had a more severe, difficult-to-treat illness with a poorer outcome compared to those with a deletion (Soni et al. 2007). However, once stability has been achieved in psychotic illness, recurrence rates are low (Larson et al. 2013). Dementias are now being documented as individuals survive into old age (Sinnema et al. 2010). Autism has been reported (Veltman et al. 2004); candidate genes for autism have been located within the 15q11-q13 region and there is evidence that those with mUPD may be more severely affected than those with a deletion (Ogata et al. 2014).

A review of the literature in order to understand how best to conceptualise behaviours and abnormal moods states associated with PWS was undertaken by Whittington & Holland (2018). Many behaviours such as eating behaviour, obsessive compulsive behaviours and skin picking, appear to have a strong genetic aetiology, whereas depression and psychosis have both genetic and environmental aetiologic components. The authors caution against using standardised diagnostic labels to describe common PWS behaviours (e.g. repetitive ritualistic behaviours typical in PWS are not equivalent to those seen in OCD) as this may lead to inappropriate treatments.

Neuropsychological characteristics

The full scale IQ is usually in the mild intellectual disability range, and a mean downward shift of approximately 40 points compared to the general population is seen (Whittington et al. 2004). Those with mUPD tend to have better verbal skills and those with a deletion have better visuo-spatial skills. Also seen are poor short-term memory, deficits in sequential processing, poor socialisation skills, deficits in comprehension, abstract reasoning, recognising emotions and appreciating the concept of time (See Whittington & Holland (2018) for a review of cognition in PWS).

Neuroimaging findings

Functional and anatomical studies have implicated a combination of subcortical and higher order structures in PWS, including those involved in processing reward, motivation, affect and higher order cognitive functions (Manning & Holland 2015).

It is generally accepted that the root of many PWS characteristics lies in the hypothalamus and recently it has been shown that the hypothalamus in PWS is small compared to typical development (Brown et al. 2022).

A study by Lukoshe et al. (2013) looked at high resolution structural magnetic resonance imaging in children with confirmed PWS. All children with PWS showed signs of impaired brain growth. Those with mUPD showed signs of early brain atrophy. In contrast, children with a deletion showed signs of fundamentally arrested, although not deviant, brain development and presented few signs of cortical atrophy. The authors suggest that there are divergent neurodevelopmental patterns in children with a deletion versus those with mUPD.

Increased brain age was seen in adults with PWS who underwent MRI scanning (Azor et al. 2019). This was independent of high BMI, or use of growth and sex hormones, and may reflect premature brain aging or abnormal brain development.

Physical health and endocrine

The most prevalent physical health problems in people with PWS are scoliosis, respiratory problems, dermatological lesions, hyperlipidaemia, hypothyroidism, Type 2 diabetes mellitus and lymphoedema (Laurier et al. 2014).

Growth hormone supplementation can increase height and the rate of growth, decrease mean body fat, improve respiratory muscle function and physical strength and improve facial dysmorphism. However, after cessation of growth hormone therapy, BMI can increase again, and long term therapy may be indicated (Oto et al. 2014). Furthermore, cessation of growth hormone therapy may lead to successive deterioration in behaviours in children with PWS (Bohm et al. 2014).

In 2021, the International Prader-Willi Organisation called for approval of Growth Hormone Replacement Therapy (GHt), not only in children with PWS but also extending throughout the lifespan (Hoybye et al). They noted that GHt was already fairly widely approved for children with PWS, beginning with the USA and EU in the 1990s. Although effects on height and early motor development were absent for obvious reasons, the benefits reported in the literature in adults with PWS were otherwise similar to those observed in children with the syndrome. In summary these are: normalisation of IGF-I levels, increase in lean body mass, decrease in body fat, improved physical fitness, and beneficial effects on cardiovascular risk markers, and on behaviour and quality of life. The authors also touched on the two contra-indications: serious sleep apnoea and untreatable diabetes mellitus, cautioning that sleep studies should be carried out before GHt can be prescribed and that GHt should not be used in people with untreatable diabetes mellitus.

A study by Cohen et al. (2014) showed that central sleep apnea with associated oxygen desaturations is more prevalent in infants compared with older children with PWS. The authors found that supplemental oxygen was efficacious in treating central sleep apnea in infants and advised routine sleep surveillance for all children with PWS with consideration given to oxygen therapy.

Symptoms of constipation are common in people with PWS with up to 40% fulfilling defined criteria for constipation in a study by Kuhlmann et al. 2014. These symptoms cannot be explained by abnormal eating habits. Gastrointestinal transit times are also increased compared with the general population and may in part be related to poor muscle tone. Studies have shown that people with PWS produce less saliva and have a high risk of choking. A pilot study by Gross et al.(2014) showed that food was visualised on x-ray, lodged in throats, but the people with PWS were unaware of it.

Osteoporosis, osteopenia and fractures are relatively common in people with PWS. Growth hormone treatment can improve bone size and strength but not bone mineral density in people with PWS (Longhi et al. 2015).

Useful websites/associations for more information

PWS Association UK: www.pwsa.co.uk

PWS Association USA: www.pwsausa.org

IPWSO (International PWS Organisation): www.ipwso.org

Online Mendelian Inheritance in Man (OMIM): www.omim.org

Updated in 2019 by Sarita Soni

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