Prader-Willi Syndrome (PWS)

First description

Prader-Willi syndrome (PWS) was first described in 1956 by Prader, Labhart and Willi.

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 *IPW* being the genes whose absence of expression at the locus 15q11-13 are considered central to PWS.** As yet, no single gene mutation has been identified as a cause of PWS, other than a mutation of the imprinting centre which itself influences the expression of several genes.

Despite significant advances in genetic testing, diagnosis is usually made clinically, and can be delayed until later in childhood. 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 29,000 and the prevalence is 1 in 52,000 (Whittington *et al*. 2001).

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).

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 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).

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.

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).

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).

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**

References

1. **Azor A.M., Cole J.H. *et al.* (2019)** Increased brain age in adults with Prader-Willi syndrome. *NeuroImage: Clinical* 21 online
2. **Boer H., Holland A., Whittington J., Butler J., Webb T. & Clarke D. (2002)** Psychotic illness in people with Prader Willi syndrome due to chromosome 15 maternal uniparental disomy. *Lancet* 359, 135-136.
3. **Böhm, B., Ritzén, E.M., Lindgren, A.C. (2014)** Growth hormone treatment improves vitality and behavioural issues in children with Prader-Willi Syndrome. *Acta Paediatr* 104 (1), 59-67
4. **Bull, L., Oliver, C., Callaghan, E., Woodcock, K.A. (2014)** Increased Exposure to Rigid Routines can Lead to Increased Challenging Behavior Following Changes to Those Routines. *Journal of Autism and Developmental Disorders* Nov 25
5. **Butler M., Hartin S.N. *et al.*(2019)** Molecular genetic classification in Prader-Willi syndrome: a multisite cohort study. *J Med Genet* 56: 148-153
6. **Clarke D.J., Boer H., Whittington J., Holland A., Butler J. & Webb T. (2002)** Prader-Willi syndrome, compulsive and ritualistic behaviours: the first population-based survey. *Br J Psychiat* 180, 358-362.
7. **Cohen M, Hamilton J, Narang I (2014**). Clinically Important Age-Related Differences in Sleep Related Disordered Breathing in Infants and Children with Prader-Willi Syndrome. *PLoS ONE* June 30, 9(6)
8. **De Waele K, Ishkanian S.L., Bogarin R., Miranda C.A., Ghatei M.A., Bloom S.T., Pacaud D., Chanoine J.P. (2008)** Long acting octreotide treatment causes a sustained decrease in ghrelin concentrations but does not affect weight, behaviour and appetite in subjects with Prader-Willi syndrome. *Eur J Endocrinol* 159, 381-8.
9. **Dykens E.M. & Kasari C. (1997)** Maladaptive behavior in children with Prader-Willi syndrome, Down syndrome and nonspecific mental retardation. *Am J Ment Retard* 102, 228-37.
10. **Goldstone A.P. (2004)** Prader-Willi syndrome: advances in genetics, pathophysiology and treatment. *Trends Endocrinol Metab* 15; 12-20.
11. **Gross, R., & Cherpes, G. (2014)** Pilot study examining swallowing function in persons with Prader-Willi syndrome. *Handout PWSA (USA)*
12. **Hinton E.C., Holland A.J., Gellatly M.S., Soni S., Patterson M., Ghatei M.A, & Owen A.M. (2005)** Neural representations of hunger and satiety in Prader-Willi syndrome. *Int J Obes (Lond)* 30(2), 313-321.
13. **Holland A.J., Treasure J., Coskeran P., Dallow J., Milton N. & Hillhouse E. (1993)** Measurement of excessive appetite and metabolic changes in Prader-WIlli syndrome. *Int J Obes* 17, 527-532.
14. **Holm V.A., Cassidy S.B., Butler M.G., Hanchett J.M., Greenswag L.R., Whitman B.Y. & Greenberg (1993)** Prader-Willi syndrome: consensus diagnostic criteria. *Pediatrics* 91, 398-402.
15. **Kuhlmann, L., Joensson I.M., Froekjaer J.B., Krogh K. & Farholt S. (2014)** A descriptive study of colorectal function in adults with Prader-Willi Syndrome: high prevalence of constipation. *BMC Gastroenterology* 14:63

16. **Larson FV, Whittington J, Webb T, Holland AJ (2013)** A longitudinal follow-up study of people with Prader-Willi syndrome with psychosis and those at increased risk of developing psychosis due to genetic subtype. *Psychological Medicine* Dec 13, 1-5
17. **Laurier, V., Lapeyrade, A., Copet, P., Demeer, G., Silvie, M., Bieth, E., Coupaye, M., Poitou, C., Lorenzini, F., Labrousse, F., Molinas, C., Tauber, M., Thuilleaux, D. and Jauregi, J. (2014)**, Medical, psychological and social features in a large cohort of adults with Prader–Willi syndrome: experience from a dedicated centre in France. *Journal of Intellectual Disability Research* 59(5), 411-421
18. **Longhi, S., Grugni, G., Gatti, D., Spinozzi, E., Sartorio, A., Adami, S., Fanolla, A., Radetti, G. (2015)** Adults with Prader-Willi Syndrome have Weaker Bones: Effect of Treatment with GH and Sex Steroids. *Calcif Tissue Int*. 96(2),160-6.
19. **Lukoshe, A., White, T., Schmidt, N., Van Der Lugt, A., and Hokken-Koelega A. C. (2013)** Divergent structural brain abnormalities between different genetic subtypes of children with Prader–Willi syndrome. *Journal of Neurodevelopmental Disorders*, 5(1), 31
20. **Mahmoud R., Singh P. *et al*. (2019)** Newborn screening for Prader-Willi syndrome is feasible: Early diagnosis for better outcomes. Am J Med Genet Part A 179A: 29-36
21. **Manning K. E. & Holland A. J. (2015)** Puzzle pieces: Neural Structure and Function in Prader-Willi Syndrome. Diseases 3(4): 382-415
22. **Miller JL & Angulo M. (2013)** An open-label pilot study of *N*-acetylcysteine for skin-picking in Prader–Willi syndrome. *Am J Med Genet* Part A 164,421–424.
23. **Ogata H, Ihara H, Murakami N, Gito M, Kido Y, Nagai T. (2014).** Autism spectrum disorders and hyperactive/impulsive behaviors in Japanese patients with Prader–Willi syndrome: A comparison between maternal uniparental disomy and deletion cases. *American Journal of Medical Genetics Part A*
24. **Oto, Y., Tanaka, Y, Abe, Y., Obata, K., Tsuchiya, T., Yoshino, A., Murakami, N. and Nagai, T. (2014).** Exacerbation of BMI after cessation of growth hormone therapy in patients with Prader–Willi syndrome. *Am J Med Genet* Part A 9999:1–5.
25. **Rice L.J., Woodcock K. & Einfeld S.L. (2018)** The characteristics of temper outbursts in Prader-Willi syndrome. *Am J Med Genet Part A* 176A: 2292-2300
26. **Sinnema M., Schrander-Stumpel C.T., Verheij H.E., Meeuwsen M., Maaskant M.S., Curfs L.M. (2010)** Dementia in a woman with Prader-Willi syndrome. *Eur J Med Genet* 53(3), 145-8
27. **Soni S., Whittington J., Holland A.J., Webb T., Maina E.N., Boer H., Clarke D. (2007)** The course and outcome of psychiatric illness in people with Prader-Willi syndrome: implications for management and treatment. *J Intellect Disabil Res* 51(1), Jan.,32-42.
28. **Soni S., Whittington J., Holland A.J., Webb T., Maina E.N., Boer H., Clarke D. (2008)** The phenomenology and diagnosis of psychiatric illness in people with Prader-Willi syndrome. *Psychol Med* 38, 1505-1514.
29. **Veltman M.W., Thompson R.J., Roberts S.E., Thomas N.S., Whittington J. & Bolton P.F. (2004)** Prader-Willi syndrome--a study comparing deletion and uniparental disomy cases with reference to autism spectrum disorders. *Eur Child Adoles Psy* 13, 42-50.
30. **Whittington J.E., Holland A.J., Webb T., Butler J., Clarke D. & Boer H. (2001)** Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK Health Region. *J Med Genet* 38, 792-798.
31. **Whittington J., Holland A., Webb T., Butler J., Clarke D. & Boer H. (2004)** Cognitive abilities and genotype in a population-based sample of people with Prader-Willi syndrome. *J Intellect Disabil Res.* 48, 172-187.
32. **Whittington J. & Holland A. (2018)** A review of psychiatric conceptions of mental and behavioural dsorders in Prader-Willi syndrome. *Neuroscience and Biobehavioral Reviews* 95: 396-405

Updated by Sarita Soni, April 2019

The SSBP strongly recommends patients to follow the advice and direction of their clinical team, who will be most able to assess their individual situation

SSBP Syndrome Sheets represent the views of the authors who kindly prepared them, and not necessarily those of the SSBP.