THELANCETDE-D-20-01059R2
S2213-8587(21)00002-4
Embargo: February 26, 2021 — 23:30 (GMT)
Doctopic: Review and Opinion

Endocrine disorders in Prader-Willi syndrome: a model to understand and treat hypothalamic dysfunction

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Prader-Willi syndrome is a rare genetic neurodevelopmental disorder resulting from the loss of expression of maternally imprinted genes located in the paternal chromosomal region, 15q11–13. Impaired hypothalamic development and function is the cause of most of the phenotypes comprising the developmental trajectory of Prader-Willi syndrome: from anorexia at birth to excessive weight gain preceding hyperphagia, and early severe obesity with hormonal deficiencies, behavioural problems, and dysautonomia. Growth hormone deficiency, hypogonadism, hypothyroidism, premature adrenarche, corticotropin deficiency, precocious puberty, and glucose metabolism disorders are the main endocrine dysfunctions observed. Additionally, as a result of hypothalamic dysfunction, oxytocin and ghrelin systems are impaired in most patients. Standard pituitary and gonadal hormone replacement therapies are required. In this Review, we discuss Prader-Willi syndrome as a model of hypothalamic dysfunction, and provide a comprehensive description of the accumulated knowledge on genetics, pathophysiology, and treatment approaches of this rare disorder.

Lancet Diabetes Endocrinol 2021
Published Online
February 26, 2021
https://doi.org/10.1016/
S2213-8587(21)00002-4

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Introduction

The first description of Prader-Willi syndrome was a two-page article published in 1956 by Andrea Prader, Heinrich Willi, and Alexis Labhart.[1] These authors described the main features of Prader-Willi syndrome as obesity, short stature, cryptorchidism, intellectual disability, and an initial phase of failure to thrive in neonates and infants (aged 0–9 months). Prader-Willi syndrome was considered a simple syndromic obesity that could be clinically diagnosed. However, knowledge has vastly expanded, and this syndrome is now known to be a rare and severe neurodevelopmental disorder that is characterised by cognitive disabilities, behavioural problems, and a specific hypothalamic dysfunction, including hyperphagia and endocrine dysfunctions. Growth hormone was the first (and is still the only) medically approved treatment for Prader-Willi syndrome in the USA and Europe. In this Review, a comprehensive description is presented of the knowledge accumulated over the past few decades, including pathophysiological insights, with a particular focus on endocrine dysfunctions.

Overview of clinical symptoms

A neurodevelopmental–endocrine–metabolic trajectory

Prader-Willi syndrome is a rare genetic neurodevelopmental condition with an estimated incidence of one in 21000 newborns.[2] A seminal publication describing the nutritional phases of this disorder improved knowledge regarding its natural history.[3] At phase 0, intrauterine growth is restricted. In phase 1 (at birth), the infant is hypotonic; subphase 1a is characterised by difficulty feeding with or without failure to thrive (aged 0–9 months), and in subphase 1b the infant grows steadily along a growth curve and weight increases at a normal rate (aged 9 months to 2 years). Phase 2 is associated with excessive weight gain, without a substantial change in appetite or caloric intake in subphase 2a (aged 2–4 years), and with a concomitant increased interest in food in subphase 2b (aged 4–6 years). Phase 3 is characterised by marked hyperphagia, typically accompanied by food seeking and insatiable appetite. Some adults progress to phase 4, and the individuals no longer have an insatiable appetite and have the ability to feel full. The mechanisms of the developmental shift observed in phase 2a are not completely understood. Concomitant to the development of nutritional phases, behavioural problems also occur, with deficits in social skills, learning abilities, and emotional control. Various comorbidities occur throughout life. This specific neurodevelopmental trajectory includes, and might be due to, abnormal development and function of the hypothalamus, and seems to explain characteristic Prader Willi syndrome phenotypes such as feeding disorders, specific behaviours, psychiatric phenotypes, and endocrine dysfunction (figure 1).

Standard dysmorphic features and natural history

The dysmorphic features of Prader-Willi syndrome include a long, narrow face, almond-shaped eyes, a down-curved mouth with a thin upper lip, and small hands and feet. In neonates, severe hypotonia, poor sucking and swallowing, and a poor appetite often lead to failure to thrive; poor social interactions are commonly observed and are also highly suggestive of Prader-Willi syndrome.[4,5] In early childhood (aged 3–4 years), the hypotonia improves but remains throughout life,[6,7] and mild to moderate intellectual disability, delayed psychomotor development, impaired growth, and abnormal body composition become increasingly apparent. The pubertal growth spurt is poor and adult height reduced. Scoliosis is reported in 23–40% of children and 70–80% of adults, with a mean age at diagnosis of 7 years. The age at diagnosis has a bimodal distribution: the first peak in early childhood (younger than 4 years) and the second in the peri-pubertal period (aged 10–13 years).[8] Occurrence of low bone mineral density and fractures are well known in Prader-Willi syndrome but are poorly documented in the literature.[9] Central and obstructive apnoea are common, as are other comorbidities. Adulthood is associated with the appearance or worsening of comorbidities, especially obesity and diabetes[10,11] (figure 2).

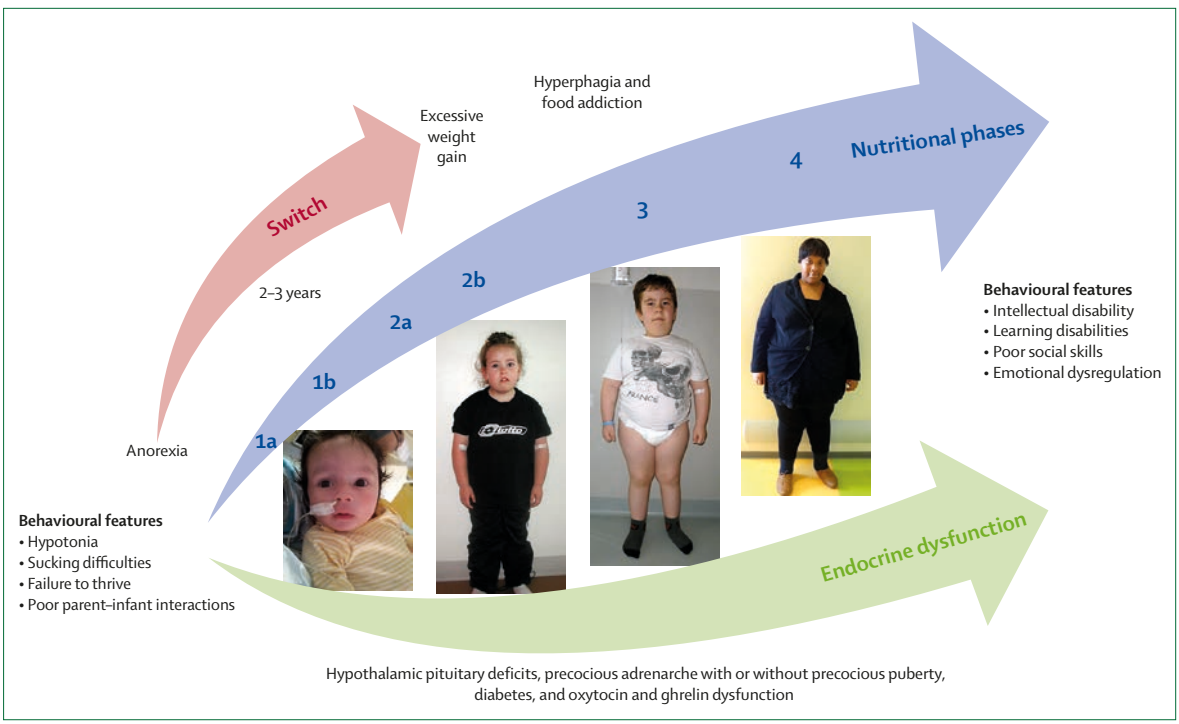

Figure 1: **Natural history of Prader-Willi syndrome**
Written informed consent was obtained from all patients or their guardians.

Specific behavioural issues

Although overeating is universally present, compulsive and ritualistic behaviours, skin picking, and some features of autism spectrum disorder are also very common in Prader-Willi syndrome. Individuals with Prader-Willi syndrome show pronounced emotional lability and an inability to control their emotions, resulting in frequent temper outbursts. Social skills are poor, with deficits in the ability to understand the emotional states of others as well as their own emotional experiences.[12] Based on clinical observations of adults, a model of the psychiatric disorders associated with Prader-Willi syndrome was defined with several psychopathological profiles: basic, impulsive, compulsive, and psychotic.[13]

A life-threatening disease throughout life

Morbidity and mortality rates of 1·25–3·00% per year have been reported despite major improvements in multidisciplinary care.[14,15] Major causes of death in individuals with Prader-Willi syndrome are respiratory diseases at all ages (more than 50% of individuals), accidents, choking related to hyperphagia, gastrointestinal perforation in adolescents and young adults, and obesity-related cardiac and respiratory failures in adults.[15,16]

Genetics

Prader-Willi syndrome was the first imprinting disorder to be identified. The syndrome results from the loss of expression of paternal genes in the Prader-Willi syndrome region (figure 3) of chromosome 15 at positions q11–13. These genes are maternally imprinted, which means they are only expressed from the paternal chromosome. Four genetic subtypes derived from distinct mechanisms have been identified: (1) paternal deletion (type I, type II, or atypical deletions of different lengths depending on the proximal chromosomal breakpoint), (2) maternal uniparental disomy, (3) rare imprinting defects, and (4) various and very rare chromosomal rearrangements, such as translocations involving the Prader-Willi syndrome region.

Currently, the diagnosis of Prader-Willi syndrome is made during the first weeks of life in a neonate presenting with severe hypotonia and feeding difficulties. Searching for an abnormal methylation profile of the *SNRPN* gene is the most appropriate genetic testing to be done. If the result is negative, the possibility of misdiagnosis is very small (less than 1%) and karyotyping is required. If the result is positive, a diagnosis of Prader-Willi syndrome is supported. Karyotyping is necessary in all situations, to recognise and identify chromosomal rearrangements and translocations involving chromosome 15. Genetic subtyping should be done as early as possible. The search for deletion in the chromosomal region 15q11–13 can be done via fluorescence in-situ hybridisation, comparative genomic hybridisation arrays, or multiplex ligation-dependent probe amplification.[18] If the results are negative, maternal disomy can be confirmed with haplotype analyses, requiring both parents' samples. If all analyses are negative, the conclusion will be that Prader-Willi syndrome

is due to an imprinting defect with epigenetics mutations. The deletion to non-deletion ratio is about 50% in neonates compared with 65% reported in the overall Prader-Willi syndrome population.[2,19] The difference in ratio is probably due to increasing maternal age at birth of the neonate with Prader-Willi syndrome.[20] Genetic counselling is useful for families affected by Prader-Willi syndrome because even though the occurrence of Prader-Willi syndrome is sporadic in more than 90% of individuals, the probability of having another child with Prader-Willi syndrome is high for parents when the child carries microdeletion of the imprinting centre (50%) or translocations (10% to 25%).[18]

Very rarely, the diagnosis of Prader-Willi syndrome is made during pregnancy. The signs are poor and non-specific, but most of them become obvious during the last trimester.[2] These include decreased foetal movements (in 27% of cases), polyhydramnios (in 17% of cases), and abnormal blood markers with ultrasound features, such as restricted intrauterine growth and abnormal hand and feet positions leading to amniocentesis (in 20% of cases).[21] If Prader-Willi syndrome is diagnosed, pregnancy termination can be discussed in some countries and carried out after ethical considerations.

Pathophysiology of Prader-Willi syndrome

Associations with the Prader-Willi syndrome phenotype

Increasing evidence from mice models and human data suggest that the complex Prader-Willi syndrome chromosomal region is crucial for the development and function of the hypothalamus. The hypothalamus is involved in homeostasis control (ie, endocrine and metabolic processes, and appetite and behaviour regulations associated with the autonomic nervous system; figure 4). Fluid balance is regulated by vasopressin secretion, and rare cases of severe hyponatraemia have been observed in people with Prader-Willi syndrome, specifically in young adults with excessive water intake who are receiving medications known to induce inappropriate secretion of antidiuretic hormone.[22]

The minimal chromosomal critical deletion associated with the Prader-Willi syndrome phenotype[23] was deduced from clinical cases with chromosomal translocations. This deletion removes *SNORD109A*, the *SNORD116* cluster (30 small nucleolar RNA copies) and *IPW* (figure 3).[17] The *SNORD116* region encodes two non-coding RNAs, the *SNORD116* small nucleolar RNAs and the spliced long non-coding RNA host gene (*116HG*) that is stably retained in the nucleus.[24] Therefore, the *SNORD116* cluster appears to drive the whole phenotype of Prader-Willi syndrome, recapitulating the natural history of the syndrome from birth to adulthood. Microdeletions of the *SNORD116* gene cluster[23,25,26] have been reported in a few patients with an almost complete Prader-Willi syndrome phenotype. Reactivation of the *Snord116* gene in the *Snord116* knockout mice model lessened the features of the Prader-Willi syndrome phenotype.[27]

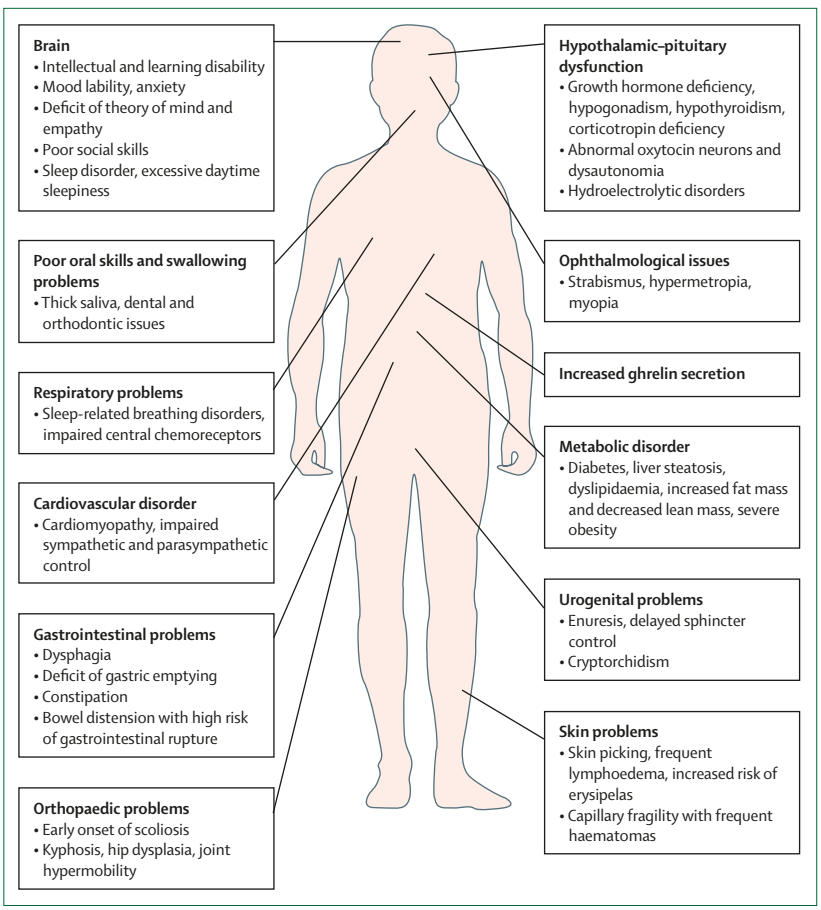

Figure 2: **Somatic and psychological problems associated with Prader-Willi syndrome are closely linked**

Individuals carrying a mutation of *MAGEL2* gene have been identified in a cohort of patients with autism spectrum disorder.[28] A new syndrome has subsequently been described and named Schaaf-Yang Syndrome.[26,29,30] In these patients, autistic features are more frequent than in patients with Prader-Willi syndrome, whereas obesity is less frequent.[28]

Notably, mutations of *MKRN3* have been reported in paternally inherited precocious puberty.[31] This gene encodes a protein that inhibits the hypothalamic gonadotropin-releasing hormone neurons through the Kisspeptin pathway during infancy and childhood, and therefore controls the onset of puberty.

The *SNORD116* gene cluster

The *SNORD116* gene belongs to the family of small nucleolar RNAs. Zhang and colleagues[32] reported in mice the expression of the *Snord116* cluster in the hypothalamus, suggesting this gene has a regulatory role in hypothalamic development and function. *Snord116* knockout mice showed short stature, hyperphagia, and decreased energy expenditure. After selective disruption of *Snord116* expression in the mediobasal hypothalamus of adult mice, obesity occurred in 10% of the mice.[33] These findings

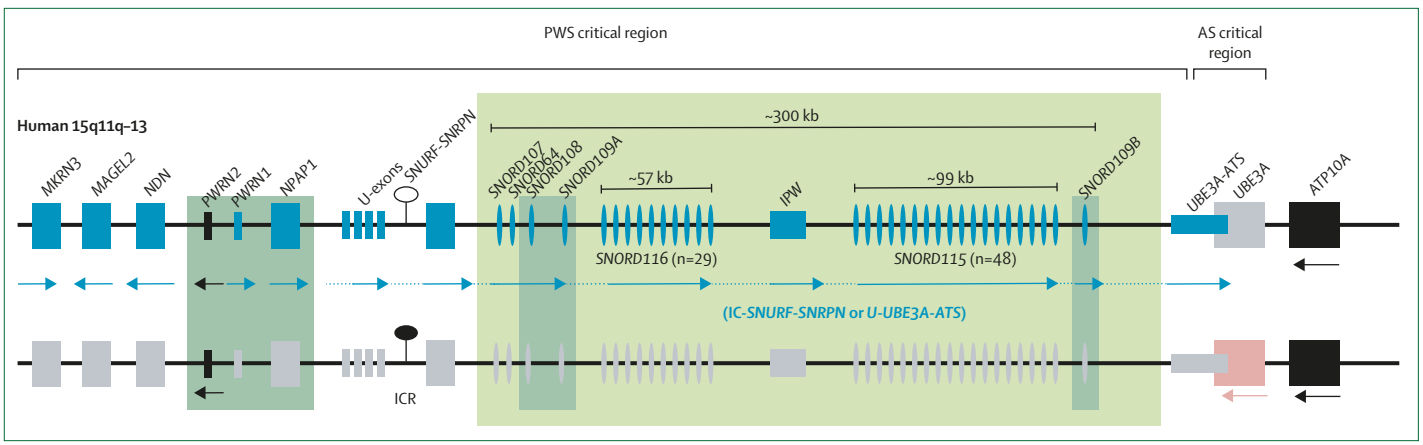

Figure 3: **Schematic physical map of the 15q11–13 chromosomal region**
Adapted from Cavaillé, 2017.[17] The paternally inherited chromosome is shown above and the maternally inherited chromosome is shown below. Alleles expressed from the paternally inherited chromosome are in blue; those expressed from maternally inherited chromosome are in pink. Silent alleles are shown in grey and non-imprinted gene loci are shown in black. The differentially methylated region imposing the mono-allelic expression of all imprinted genes over the entire domain (the ICR) is shown by filled and non-filled lollipop shapes (methylated and unmethylated, respectively). The *SNORD* gene array (oval shapes) is highlighted by the green box; dark green boxes denote gene loci that are not conserved between mouse and human. AS=Angelman syndrome. ICR=imprinting centre region. PWS=Prader-Willi syndrome.

suggest that the *Snord116* gene cluster controls hyperphagia and obesity.

Hypothalamic neurons collected from redifferentiated induced pluripotent stem cells from patients with either Prader-Willi syndrome or an *SNORD116* microdeletion showed a deficit in prohormone processing.[34] The patients showed reduced expression of transcription factor NHLH2 that decreases the transcription of the *PCSK1* gene coding for neuroendocrine convertase 1. In *Snord116* knockout mice, pro-insulin, pro-growth hormone-releasing hormone, and pro-ghrelin processing were impaired. Therefore, neuroendocrine convertase 1 deficiency might drive the major neuroendocrine phenotype of Prader-Willi syndrome. Furthermore, evidence is emerging that diurnal or circadian disruptions could be involved in the pathogenic mechanism of Prader-Willi syndrome.[35]

The *MAGEL2* gene

In both humans and mice, *MAGEL2* mutations reproduce the first phase of Prader-Willi syndrome,[36] which includes neonatal hypotonia, feeding difficulties, and multiple pituitary hormone deficits, and social and learning difficulties in adults. *Magel2* knockout mouse models show an alteration in the development, function, and maturation of oxytocin neurons[37,38] and a decreased density of anorexigenic α-melanocyte-stimulating hormone axons, probably due to the alteration in the direct neurotrophic effect of MAGE-like protein 2.[39]

Brain imaging abnormalities

Pituitary hypoplasia has been observed in 63–74% of patients with Prader-Willi syndrome, and many also show an abnormal posterior pituitary bright spot and reduced hypothalamic perfusion on MRI.[40,41] Additionally, a 2019 study reported that brain age was increased by almost 8·7 years in young adults with Prader-Willi syndrome compared with age-matched and sex-matched controls.[42] Functional neuroimaging studies have reported abnormalities in the subcortical and cortical structures involved in eating and behaviour in patients with Prader-Willi syndrome.[4]

Endocrinology of obesity and appetite dysregulation in Prader-Willi syndrome

Characterisitcs of the obesity in Prader-Willi syndrome

Prader-Willi syndrome is the most common genetic obesity syndrome. The frequency of obesity caused by hyperphagia varies from 40% in children to 82–98% in adults. The distress for patients and their caregivers is lifelong, considering that hyperphagia requires constant diet restriction, environmental controls, and supervision; quality of life, social function, school, and work are affected.[4,12,43] As shown in a previous study,[43] Prader-Willi syndrome substantially affects the individual themselves, the family, and the caregivers. Notably, the negative affect of the symptoms of Prader-Willi syndrome increases over time, with most caregivers caring for individuals over the age of 12 years reporting moderate to severe affects, with short-term and long-term consequences.[43] A 2020 publication argues that hyperphagia in Prader-Willi syndrome might be linked with addiction for food.[44]

The body composition in Prader-Willi syndrome is abnormal and independent of the presence of obesity. Many studies that used dual-energy x-ray absorptiometry as the reference method have reported that children[45,46] and adults[47–50] with Prader-Willi syndrome have altered body composition, with increased adiposity and reduced muscle mass compared with BMI-matched controls. Additionally, adults with Prader-Willi syndrome have a specific fat distribution, with increased appendicular fat mass and decreased trunk fat mass.[51] However, data for the visceral

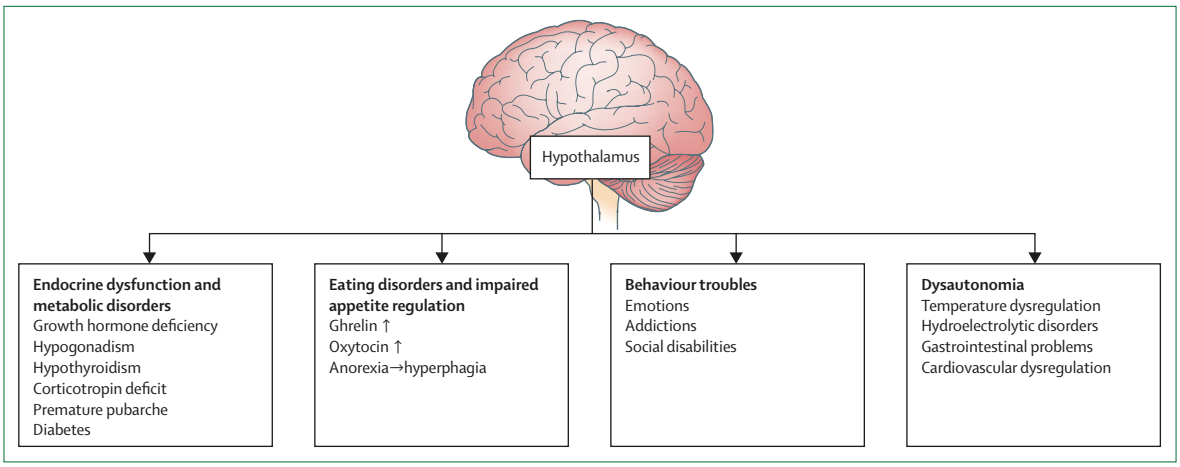

Figure 4: **Impaired development and function of the hypothalamus explains most of the typical features of Prader-Willi syndrome**
The hypothalamus controls endocrine and metabolic function, appetite regulation, emotion, and behaviour and is linked to the autonomic nervous system. Impaired development and function of the hypothalamus explains most of the typical features of Prader-Willi syndrome.

fat quantity of patients with Prader-Willi syndrome have been discordant[52,53] compared with data for patients who have obesity and have been matched for BMI, sex, and age. Several,[53–55] but not all,[56] studies have reported that patients with Prader-Willi syndrome have a better metabolic profile—ie, lower insulin resistance—than individuals with primary obesity when matched according to BMI or body fat percentage. Whether the genotype could influence the metabolic profile is still a matter of debate.[53,54,56] Few studies have compared BMI and body composition between the two main genetic subtypes (deletion *vs* maternal uniparental disomy) in children and adolescents[57,58] and in adults.[54,59] All authors reported similar BMI and body fat percentage results between the two genetic subtypes; however, sample sizes were relatively small (n=50). In a large cohort of 154 patients with Prader-Willi syndrome, adults with a deletion were reported to have a higher BMI than those without a deletion.[60] In patients with uniparental disomy, a relatively higher fat mass:lean body mass ratio,[61] decreased HDL-cholesterol[56,61] and higher waist-to-hip ratio,[53] compared with patients with a deletion, suggested differences in mechanisms relating to fat distribution between the two genetic subtypes.

The roles of oxytocin and ghrelin

Oxytocin is a neuropeptide produced in the hypothalamic paraventricular nucleus and supraoptic nucleus by magnocellular and parvocellular neurons. As a hormone, oxytocin is released from the posterior pituitary and controls uterine contractions and milk ejection in women before and after birth. As a neuromodulator, oxytocin has anorexigenic effects, controls satiety, and decreases sugar intake. Substantial evidence has also suggested that oxytocin is involved in complex social and stress behaviours.[62,63]

The first data investigating the role of oxytocin in Prader-Willi syndrome were reported in 1995 by histoimmunological studies showing a reduction in oxytocin-secreting neurons (number and volume) in the paraventricular nucleus of adults with Prader-Willi syndrome versus controls.[64] Despite some contradictory results, plasma oxytocin concentrations appear to be increased in the cerebrospinal fluid of patients with Prader-Willi syndrome.[65,66] Abnormal development[37] and function of oxytocin neurons were reported in *Magel2*[38] and *Necdin*[67] knockout mice; the studies showed an increased number of oxytocin receptors in brain regions implicated in social behaviour versus wild-type mice.[38] In the *Magel2*-deficient mouse model of Prader-Willi syndrome,[38,68] oxytocin administration within 5 h after birth restored sucking and, from a long-term perspective, normalised learning, memory, and social cognition through the normal development of the oxytocin system. In infants with Prader-Willi syndrome, intranasal administration of oxytocin within 6 months of age improved oral and social skills versus baseline.[69] Treatment with oxytocin later in life has been shown to have less consistent effects, possibly due to overdosing and the use of inadequate psychometric measures.[70]

Ghrelin is mainly produced and secreted by the oxyntic glands of the gastric mucosa. Before secretion, des-acyl ghrelin is acylated by the transmembrane enzyme ghrelin-O-acyltransferase.[71] This acylated form of ghrelin, also called the hunger hormone, is considered the active form that binds GHSR1a to its receptors. Unacylated ghrelin also circulates and is acknowledged to have specific effects, opposite to those of acylated ghrelin. The hypothalamus is the main site for most of ghrelin's metabolic actions after crossing the blood–brain barrier. The initial findings describing ghrelin's induction of neuropeptide Y and agouti-related peptide release in the arcuate nucleus have been expanded in recent years. Ghrelin is also able to stimulate food intake through its actions on alternative brain systems not involving the

	Oxytocin	Ghrelin
Behavioural problems		
Emotional liability and poor emotional understanding and control	Yes	No
Deficits in social skills, absence of empathy, and poor theory of mind	Yes	No
Anxiety, repetition, stereotypical behaviour	Yes	Yes
Spatial memory	Yes	Yes
Learning disabilities	Yes	No
Untrusting of others	Yes	Yes
Temper tantrums	Yes	No
Eating disorders		
Obsession with food, meal anticipation	No	Yes
Food craving, foraging, and storing	No	Yes
Preference for sugar	Yes	No
Prolonged duration of meal	Yes	No
Deficit of satiety	Yes	No
Brain expression profile of receptors		
Expression in hippocampus, paraventricular nucleus, amygdala, and piriform cortex	Yes	Yes

Table: **Roles of oxytocin and ghrelin in the pathophysiology of Prader-Willi syndrome**

arcuate nucleus, such as the dopamine, serotonin, opioid, and cannabinoid systems. The interaction between the dopamine system and ghrelin to modulate reward and motivation[72] and to modulate the activity and synaptic input of midbrain dopamine neurons promote appetite.[73]

Since the first publications in 2002,[74] studies have consistently supported total hyperghrelinaemia in Prader-Willi syndrome at all ages.[75–78] Prader-Willi syndrome is uniquely characterised by early onset severe obesity with hyperghrelinaemia.[79] The increased total ghrelin concentration in patients with Prader-Willi syndrome is linked to high concentrations of acylated ghrelin with a relative deficit of unacylated ghrelin concentrations and a high acylated ghrelin to unacylated ghrelin ratio.[77] This finding prompted the first study to use a synthetic unacylated ghrelin analogue (AZP531/livoletide) in Prader-Willi syndrome and the report of short-term (after 2 weeks) positive results on hyperphagia in a phase 2b clinical trial.[80] Conversely, hyperghrelinaemia in infants with Prader-Willi syndrome is due to increased unacylated ghrelin concentrations, compared with that of age-matched controls,[78] with a relative excess of unacylated ghrelin. Notably, total increased ghrelin concentrations with normal acylated ghrelin concentrations were also reported in *Magel2*[39] and *Snord116*[81] knockout mice.

There is a close crosstalk between oxytocin and ghrelin, and it is difficult to separate their respective effects (table). Interestingly, the rescue of high lethality rate by neonatal administration of oxytocin in *Magel2* knockout pups was also reported in *Snord116* knockout pups with postnatal administration of a ghrelin analogue.[82] In infants with Prader-Willi syndrome, we reported that early administration of oxytocin significantly increased circulating acylated ghrelin concentrations compared to the concentrations before treatment.[69] Ghrelin receptor and oxytocin receptor heterocomplexes have been reported in some brain regions and impair oxytocin-mediated signalling and trafficking in cell cultures.[83]

Other neuropeptides involved in the regulation of appetite and satiety

Pancreatic polypeptide and brain-derived neurotrophic factor concentrations are consistently abnormal in individuals with Prader-Willi syndrome.[84,85] Fasting pancreatic polypeptide concentrations have been shown to be normal or more often reduced in Prader-Willi syndrome, whereas postprandial concentrations of pancreatic polypeptide are low. With regard to ghrelin, its action requires an intact vagal nerve reflex and it is involved in regulating gastric emptying. Low circulating brain-derived neurotrophic factor concentrations have been observed in individuals with Prader-Willi syndrome compared with individuals with obesity, and might contribute to the increased hunger in Prader-Willi syndrome.[85] Total and free leptin concentrations are increased in individuals with Prader-Willi syndrome, similarly to what is observed in weight-matched controls and without relation to the different eating phases.[84] The concentrations of neuropeptide Y, agouti-related protein, and hypocretins in individuals with Prader-Willi syndrome have been reported to be similar to healthy controls.[86] Fasting cholecystokinin concentrations are reported to be either normal or increased in Prader-Willi syndrome, and similar concentrations are reported in response to a meal.[87] Fasting and postprandial values of peptide YY concentrations have been reported to be low, normal, or high in Prader-Willi syndrome.[87,88] Fasting and postprandial glucagon-like peptide-1 concentrations in adults with Prader-Willi syndrome are similar to those concentrations in individuals with obesity and lean controls.[88] High obestatin concentrations have been reported in infants with Prader-Willi syndrome.[89]

Endocrine dysfunction in Prader-Willi syndrome

Growth hormone

Impaired intrauterine and postnatal growth rate, short stature, acromicria and hypotonia, abnormal body composition, and low energy expenditure are characteristic clinical features of Prader-Willi syndrome and are similar to those clinical features seen in patients who have growth hormone deficiency without Prader-Willi syndrome. Multiple studies of children with Prader-Willi syndrome have shown reduced growth hormone responses to stimulation tests in 80% of the individuals,[90–93] as well as decreased spontaneous growth hormone secretion and low IGF1 values (in almost 100% of individuals). Prevalence of growth hormone deficiency after completion of growth ranges from 25% to 70%.[11] Between 0% and 70% of adults with Prader-Willi syndrome fulfil the criteria for severe adult growth hormone deficiency.[94,95] Few studies have shown a higher incidence of growth hormone deficiency in patients with uniparental disomy versus patients with deletion.[96] Growth hormone deficiency might result from

decreased maturation of growth hormone-releasing hormone neuropeptides due to a defect of neuroendocrine convertase 1.[34] The hypothalamic dysfunction in Prader-Willi syndrome is permanent, and the multisystemic nature of the disease necessitates different tests and interpretations of test results, compared with those in a typical population of patients with growth hormone deficiency.

Growth hormone treatment

A seminal review on growth hormone treatment in Prader-Willi syndrome was published in 2013.[93] Treatment is now usually initiated between 3 months and 12 months of age. Several studies of infants and children with Prader-Willi syndrome have shown improvements in height, head circumference, facial appearance, BMI, body composition (with decreased fat tissue accumulation and delayed lean body mass loss), motor and cognitive development (if treatment is started in the first year of life) and socialisation with growth hormone treatment. Overall, growth hormone treatment changes the natural history of the disease; with treatment, toddlers and children with Prader-Willi syndrome are now lean in 50% of cases and young adults are leaner and have less comorbidities.[45,60,92] The effect of growth hormone treatment on adipose tissue has been reported in young children, with normalisation of β-adrenergic lipolysis and the number of adipocyte precursors.[97] Long-term studies have shown a maintained positive effect on height, body composition, metabolic status, diabetes prevalence, and hypertension[11,98] despite interruption of growth hormone treatment.[49,99,100]

To our knowledge, only one study has reported the negative effects of discontinuing growth hormone treatment in the transition phase to adulthood, with an increase in body fat and a decrease in lean body mass shown without treatment versus continued treatment.[101] Resuming growth hormone treatment completely reversed the negative effects of discontinuing treatment at completion of growth. A 2020 study supports the remaining positive effects after 3 years of follow-up in young adults.[102] Clinical trials of growth hormone treatment of adults with Prader-Willi syndrome who were not treated with growth hormone during childhood have reported improvements in body composition, with an increase in lean body mass and a reduction in total, subcutaneous and visceral fat.[10,93] The positive effects on body composition were also noted in a small observational study of adults with Prader-Willi syndrome who were treated with growth hormone for 15 years, showing sustained positive effects independent of whether growth hormone treatment was initiated in childhood or adulthood.[99]

Quality of life in adults with Prader-Willi syndrome, although difficult to evaluate, was improved with growth hormone treatment, and so was general wellbeing.[93,103] Conversely, a substantial impairment in psychosocial function was reported when growth hormone treatment was discontinued. Only one study evaluated the effect of growth hormone treatment on neuropsychological test results in adults with Prader-Willi syndrome, showing improved mental speed and cognitive flexibility versus placebo.[104]

Growth hormone treatment in children with Prader-Willi syndrome is safe, and no increased risk of diabetes, scoliosis, or central and obstructive apnoea have been observed.[105] One study reported a higher risk of leukaemia and lymphoma in patients with Prader-Willi syndrome[106] that was not related to growth hormone treatment. However, studies of sufficient statistical power and duration do not exist, but given the rarity and symptoms of Prader-Willi syndrome, such studies might be difficult to carry out.

Gonadal dysfunctions

Hypogonadism is the most common hormone deficiency in Prader-Willi syndrome, with expression in both sexes and at all ages. At birth, most boys (92·7–100%) have bilateral or unilateral cryptorchidism[107–109] and girls show signs of hypoplasia of the labia minora.[108] A normal mini-puberty was reported in two studies of infants with Prader-Willi syndrome with or without cryptorchidism.[110,111]

Previous studies have shown, in both sexes, a continuum from central to peripheral hypogonadism, with a high frequency of peripheral hypogonadism, combinations between the two forms, and a pure hypothalamic deficit (central hyogonadism) in only a few cases.[109,112] Puberty typically starts late and is incomplete in individuals with Prader-Willi syndrome.[108,113] Very few cases of early puberty have been reported, with many of them associated with premature or aggressive pubarche, or both.[114,115]

In most male individuals with Prader-Willi syndrome, testicular histology has shown reduced numbers or absence of spermatogonia; only in a few cases has the presence of spermatogonia been reported.[116] A progressive degeneration of germ cells during puberty is anticipated. In female patients with Prader-Willi syndrome, either the absence of follicle development or normal ovary histology were observed, with low to normal concentrations of inhibin B reported in a few individuals, indicating possible fertility and the importance of measuring inhibin concentrations.[108,113]

Sex-steroid treatment and fertility

Puberty is usually induced with sex steroids at normal pubertal age. There is no consensus on managing hypogonadism in Prader-Willi syndrome. Therefore, an individualised approach is important. Only one open-label trial with low-dose intramuscular testosterone (125 mg per month in 24 months) was implemented in male individuals with Prader-Willi syndrome, reporting improved secondary sex characteristics and body composition, and no negative effects on behaviour.[117] No systematic trials on sex steroid treatment have been published for women with Prader-Willi syndrome, although oestrogens and progestin are routinely prescribed for adolescents

with Prader-Willi syndrome.[108] Due to the paucity of studies, it is not known if the sex steroid treatment should aim at full replacement or if lower doses are sufficient to obtain desired clinical endpoints. In this context, it should be noted that there are narratives of rare cases of treatment of sex steroids in male individuals with Prader-Willi syndrome contributing to mood and behaviour problems.

Despite hypogonadism, individuals with Prader-Willi syndrome often express romantic thoughts, an interest in sexual experiences, and strong desires to have children. No known male individual with Prader-Willi syndrome has fathered a child, but four spontaneous and uncomplicated pregnancies were published in three women with Prader-Willi syndrome[118] Additional evidence of pregnancy in women with Prader-Willi syndrome exists but to the best of our knowledge it is not published. All children were born by caesarean section. The mothers did not breastfeed or bond with the children, who were taken care of by others. Common to all seems to have been the incapacity to put the needs of the child ahead of personal needs and desires. The genetics of the children varied. Three children had normal genetic results and one had Angelman syndrome. More pregnancies in women with Prader-Willi syndrome have probably occurred, but to the best of our knowledge these have not been published.

Premature adrenarche

Premature adrenarche is reported in up to 30% of both male and female individuals with Prader-Willi syndrome, with early appearance of pubic hair, increased serum dehydroepiandrosterone sulphate or serum dehydroepiandrosterone, and advanced bone age, which might decrease the positive effect of growth hormone on adult height.[119] No treatment is available, although a double-blind, placebo-controlled study with the aromatase inhibitor anastrozole is ongoing in children with Prader-Willi syndrome (NCT01520467).

Thyroid hormones

The prevalence of hypothyroidism in Prader-Willi syndrome has been reported, with variations of 2–4% to 14–30%,[92,120,121] and one study reported a prevalence of 72% in infants.[122] Central hypothyroidism was the most frequent cause.[121] Thyroid function testing is required at routine visits, particularly before starting growth hormone treatment and during follow-up of growth hormone treatment,[123] so that levothyroxine can be started if indicated.

Central adrenal insufficiency

The first study on central adrenal insufficiency in 2008 showed an insufficient adrenocorticotropic hormone response to a metyrapone test in 15 (60%) of 25 children with Prader-Willi syndrome.[124] However, subsequent studies in children and adults used different stimulation tests, including the insulin tolerance test, glucagon stimulation and adrenocorticotropic hormone stimulation tests, and metyrapone testing; much lower rates of central adrenal insufficiency were reported, ranging from 0% to 14%.[125] Thus, clinically relevant hypocortisolism appears to be rare with no need for hydrocortisone supplementation in the absence of clinical manifestation and confirmation of adrenal insufficiency.

Glucose metabolism

Hypoglycaemia in infants with Prader-Willi syndrome

Although rarely reported, one study shows a high frequency of hypoglycaemia during infancy, with poor clinical signs (eg, seizures or cyanosis) possibly related to some degree of hyperinsulinism that recovered with glucose supplementation.[126]

Diabetes

Several studies have reported higher insulin sensitivity in Prader-Willi syndrome compared with BMI-matched children and adults.[52,127] Other studies have shown a decreased insulin response to glucose stimulation in patients with Prader-Willi syndrome versus controls.[128] The impaired processing of proinsulin to insulin might partly explain these findings,[34] and the role of an impaired ghrelin system deserves further investigation. Diabetes is very rare in children with Prader-Willi syndrome with or without growth hormone treatment,[10,92] but glucose metabolism does worsen in these individuals during the transition phase to adulthood.[10,60,129,130] One study reported a high prevalence (24%) of impaired glucose metabolism in a large population of Prader-Willi syndrome (274 patients) that appeared to be more common in adults with obesity.[10] Preventing obesity was shown to be most important to decrease the risk for type 2 diabetes, and sex, genotype, and growth hormone treatment did not impair glucose metabolism in adults with Prader-Willi syndrome in univariate and multivariate analyses. Similar to individuals without Prader-Willi syndrome, diagnosing and monitoring of type 2 diabetes in individuals with Prader-Willi syndrome should follow general guidelines. The use of metformin in Prader-Willi syndrome has been poorly documented in the literature. One study in non-diabetic children and adolescents with obesity suggested that metformin treatment might improve sense of satiety and decrease anxiety about food in some individuals with Prader-Willi syndrome.[131] A case report of 4 months of metformin treatment showed improved glycaemic control and 20 kg weight reduction in a boy aged 13 years with Prader-Willi syndrome and type 2 diabetes.[132] Nevertheless, difficulties in compliance to diet and food compulsivity, together with sweet food preference, explain very high plasma concentrations of HbA_{1c} and glucose in some patients, leading to severe uncontrolled diabetes. In these situations, the use of sodium-glucose cotransporter-2 inhibitors in combination with glucagon-like peptide-1 receptor agonists offers new perspectives on normalisation of HbA_{1c} and plasma glucose[133] combined with weight loss. However, the combination of delayed gastric emptying caused by

Search strategy and selection criteria

Relevant articles published in English were searched for between June 1, 2018, and June 30, 2020, on PubMed and Medline. We used the term "Prader-Willi syndrome" in the medical subject heading and in several subheadings related to the subchapters of the review. Additionally, since 2008, we have collected all publications on Prader-Willi syndrome (more than 10 000 articles). MT is currently updating the French protocole national de diagnostic et de soins on Prader-Willi syndrome and has reviewed literature from 2012 to 2020, including 150 papers on the endocrine aspects of Prader-Willi syndrome.

glucagon-like peptide-1 receptor agonists and the pre-existing risk of gastric rupture in Prader-Willi syndrome require particular attention, although it should be noted that no gastrointestinal complications with glucagon-like peptide-1 receptor agonists have been reported in patients with Prader-Willi syndrome.

Conclusions

There is now extensive knowledge about Prader-Willi syndrome with regards to its natural history, pathophysiology, genetics, and the associated endocrine defects due to hypothalamic dysfunction. Impaired oxytocin and ghrelin systems described in this rare disease and the perspective of compensating these hormonal defects might change the current diagnosis and therapeutic approaches of other hypothalamic diseases. Growth hormone treatment has substantially changed the clinical characteristics of children and adults with Prader-Willi syndrome and is now started early in life, resulting in improved cognition and socialisation. Optimising the treatment of hypogonadism is necessary, as are studies on affective issues and sexuality. Several trials on the treatment of hyperphagia are ongoing, and hopefully their findings will lead to advances to substantially modify the drive to eat, thereby reducing the risk of severe obesity and its comorbidities, and decreasing distressing behaviours. These potential findings might also apply to other conditions with severe obesity, including hypothalamic obesity.

Contributors

MT and CH contributed equally to the bibliographical search, the drafting, and the final writing of the Review.

Declaration of interests

MT has a patent (PCT/EP2011/058590) licensed to OT4B and was a member of Millendo Therapeutics and Helsinn Healthcare for ghrelin analogue treatment in Prader-Willi syndrome. CH has acted as an investigator and is a member of the global steering committee for Sandoz' PATRO adult study on growth hormone treatment in adults with Prader-Willi syndrome.

Acknowledgments

We want to acknowledge the members of the scientific advisory board of International Prader-Willi Syndrome Organization for interesting discussions over the many years: Susanne Blichfeldt, Suzanne B Cassidy, Daniel J Driscoll, Marilyn C Dumont-Driscoll, Urs Eiholzer, Janice L Forster, Ann Scheimann, and Harold JP Van Bosse.

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