Approach to the Child with Prader-Willi Syndrome

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Prader-Willi syndrome (PWS) is a complex genetic disorder that is caused by the absence of normally active paternally expressed genes from the chromosome 15q11-q13 region (1). PWS has a prevalence of 1/10,000 to 1/30,000 individuals and is characterized by poor feeding in infancy often associated with failure to thrive, followed by obesity beginning around age 2 (1, 2). These individuals also have hyperphagia, hypotonia, developmental and cognitive delay, behavioral problems, and neuroendocrine abnormalities. Hypogonadism is present in both males and females and manifests as genital hypoplasia, incomplete pubertal development, and, in most, infertility. Short stature is common, related to GH insufficiency. Characteristic facial features, strabismus, and scoliosis are often present, and there is an increased incidence of sleep disturbance and type II diabetes mellitus, the latter particularly in those who become obese.

The Case

A 3-month-old infant admitted to the hospital for evaluation of failure to thrive is found to have PWS by DNA methylation testing. History reveals that he was born via emergency cesarean section at 37 wk gestational age after a pregnancy complicated by polyhydramnios and decreased fetal movements. He was unable to breast feed due to poor suck but was able to take 2 ounces of formula over 30 min using a widened, fast-flow nipple. He was discharged home with his parents, but was readmitted for failure to thrive when he was 3 months old. On physical examination at admission, he was noted to have almond-shaped eyes, bitemporal narrowing, a thin upper lip with downturned corners of the mouth, decreased muscle mass,

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2012–2543 Received June 19, 2012. Accepted October 5, 2012.

Abbreviations: CAI, Central adrenal insufficiency; PWS, Prader-Willi syndrome; REM, rapid eye movement.

and a hypoplastic scrotal sac with bilateral undescended testes. This case will be used to illustrate the range of issues associated with PWS and the recommendations and controversies surrounding treatment. Specific issues to be addressed include GH treatment, additional endocrinopathies seen in individuals with PWS, the various nutritional phases that individuals with PWS go through, and recommendations for weight control.

Background

PWS is an imprinted condition, with approximately 70% of the cases due to a *de novo* deletion in the paternally inherited chromosome 15 q11-q13 region, 25% from a maternal uniparental disomy of chromosome 15, and the remaining 5% from either microdeletions or epimutations of the imprinting center in the 15q11-q13 region (*i.e.* imprinting defects) (3, 4). The absence of expression of one or more of the paternally inherited genes must contribute to the phenotype of PWS, but at the current time the exact function of each of the genes in determining the PWS phenotype remains to be elucidated. No single gene mutation has been found in humans that explains all the features of this syndrome.

Diagnosis

Although published consensus clinical diagnostic criteria are available and accurate, the mainstay of diagnosis is genetic testing. DNA-based methylation testing will detect abnormal parent-specific imprinting within the Prader-Willi critical region on chromosome 15. This testing determines whether the region is maternally inherited only (*i.e.* the normal paternal imprint is absent) and detects over 99% of affected individuals. Diagnosis can also be made by fluorescence *in situ* hybridization or chromosomal microarray for patients who have deletion of chromosome 15q11.2-q13. Angelman syndrome must be in the differential diagnosis for individuals who have a deletion of chromosome 15q11.2-q13, and DNA methylation testing must be done to confirm the diagnosis of PWS. DNA polymorphism analysis can be used to test for uniparental disomy, but blood from both parents and from the affected child is necessary for this testing. Blood from both parents and the child must be sent to an experienced referral lab for testing for an imprinting center microdeletion. This genetic testing is important to confirm the diagnosis of PWS in all individuals, but it is especially important in those who do not manifest the classic clinical features of PWS or are too young to manifest sufficient features to make the diagnosis with certainty on clinical grounds. Additionally, elucidating the specific genetic cause of PWS is important for counseling regarding recurrence risk because the recurrence risk for spontaneous deletions or uniparental disomy is low (<1%), whereas some cases of imprinting mutation have a recurrence risk of up to 50%.

Manifestations and Natural History

Prenatal characteristics

The birth weight, length, and body mass index of infants with PWS is 15–20% smaller than their unaffected siblings (although often still in the normal range), indicating that growth is abnormal prenatally (5). Prenatal hypotonia usually results in decreased fetal movement, an increased incidence of abnormal fetal position at delivery, and a need for assisted delivery or cesarean section (6).

Neonatal characteristics

Infantile hypotonia is a nearly universal finding, causing decreased movement with decreased spontaneous arousal, weak cry, and poor reflexes, including a poor suck. The hypotonia is central in origin, and neuromuscular studies including muscle biopsy, when done for diagnostic purposes, are generally normal or show nonspecific signs of disuse. In general, muscle biopsy should not be done in an infant with central hypotonia unless genetic testing has ruled out PWS. The poor suck and lethargy result in failure to thrive in early infancy, and gavage feeding or the use of special nipples is generally required for a variable period of time, usually weeks to months (5). By the time the child is drinking from a cup or eating solids, a period of approximately normal eating behavior occurs. The hypotonia improves over time, but even adults remain mildly hypotonic with decreased muscle bulk and tone.

Childhood characteristics

Delayed motor development is present in the great majority of children with PWS, with average early milestones achieved at about double the normal age (*e.g.* sitting at 12 months, walking at 24 months). Language milestones are also typically delayed. Although a small proportion of affected individuals have extremely impaired language development and apraxia, verbal ability is a strength for most; however, articulation abnormalities are frequent. Intellectual and/or learning disabilities are generally evident by the time the child reaches school age and are of variable degrees, with some children having normal IQ levels whereas others are more severely affected.

Nutritional phases

In contrast to the long-held view that there are two distinct nutritional phases in PWS, failure to thrive fol-

lowed by "hyperphagia leading to obesity," a recent collaborative study found that the transition between nutritional phases is much more complex, with seven different nutritional phases through which individuals with PWS typically progress (5) (Table 1). Phase 0 occurs *in utero*, with decreased fetal movements and growth restriction compared with unaffected siblings. In Phase 1, the infant is hypotonic and not obese, with subphase 1a characterized by difficulty feeding with or without failure to thrive (ages birth to 15 months; median age at completion, 9 months). This phase is followed by subphase 1b when the infant grows steadily along a growth curve and weight is increasing at a normal rate (median age of onset, 9 months; range, 5–15 months). Phase 2 is associated with weight gain; in subphase 2a, the weight increases without a significant change in appetite or caloric intake (median age of onset, 2.08 yr), whereas in subphase 2b the weight gain is associated with a concomitant increased interest in food (median age of onset, 4.5 yr). Phase 3 is characterized by hyperphagia, typically accompanied by food seeking and lack of a sense of satiety (median age of onset, 8 yr). Not all individuals with PWS go through all the stages described above, but the vast majority do. In addition, some adults progress to phase 4, which is when the individual no longer has an insatiable appetite and is able to feel full.

Because PWS is now typically diagnosed in infancy, parents can be provided with prospective advice on these nutritional phases. Frequent monitoring of length and weight during infancy and early childhood can help ameliorate the failure to thrive in early infancy as well as the obesity when the children get older. When increasing weight gain without a change in calories is noted (phase 2a), a well-balanced diet consisting of 30% fat, 45% carbohydrates, and 25% protein helps decrease the rate of weight gain (7) because research indicates that during phase 2a, metabolism changes from normal to increased conversion of carbohydrates to adipose tissue (5).

TABLE 1. Nutritional phases in PWS[a]

Phase	Median ages	Clinical characteristics
0	Prenatal to birth	Decreased fetal movements and lower birth weight than sibs
1a	0–9 months	Hypotonia with difficulty feeding and decreased appetite
1b	9–25 months	Improved feeding and appetite and growing appropriately
2a	2.1–4.5 yr	Weight increasing without appetite increase or excess calories
2b	4.5–8 yr	Increased appetite and calories, but can feel full
3	8 yr to adulthood	Hyperphagic, rarely feels full
4	Adulthood	Appetite is no longer insatiable

[a] Modified from J. L. Miller *et al.*: Nutritional phases in Prader-Willi syndrome. *Am J Med Genet A* 155A:1040–1049, 2011 (5), with permission. © Wiley Periodicals Inc.

Therapeutic Strategies

PWS is associated with a number of endocrinopathies, developmental, and behavioral issues that must be evaluated and treated. If possible, children with PWS should be treated in a multidisciplinary center familiar with the myriad of issues that must be addressed in the syndrome (8). Families are encouraged to network with one another via the parental support groups available through the Prader-Willi Syndrome Association.

Associated Endocrinopathies

Individuals with PWS can have a number of endocrinopathies associated with hypothalamic-pituitary insufficiency. It is recommended that endocrinologists monitor for these endocrine disorders both clinically and biochemically. Timing of testing for these hormonal abnormalities varies between physicians but can be driven by clinical symptoms.

GH deficiency

Short stature may be apparent in childhood and is almost always present by the second decade in the absence of GH replacement. The lack of a pubertal growth spurt and GH insufficiency result in an average untreated height of 155 cm for males and 148 cm for females (9). Data from at least 15 studies involving more than 300 affected children document reduced GH secretion in PWS. Best practice in early intervention for PWS recommends that GH therapy be discussed at the time of diagnosis (8). GH therapy decreases fat mass and increases muscle mass. Preliminary data also suggest that it may have a beneficial effect on weight gain, and possibly appetite, in individuals with PWS, and perhaps more importantly, an improvement in cognitive function (8, 10). Infants with PWS treated with GH therapy and multidisciplinary care have improvements in head circumference, height, body mass index, body composition (with improvement of lean muscle mass and delay of fat tissue accumulation), body proportions, acquisition of gross motor skills, language acquisition, and cognitive scores (8, 10–14). Older children and adolescents treated with GH therapy not only have the abovementioned physical benefits of the treatment but are also reported to have improvements in behaviors with lack of behavioral deterioration during adolescence. Children

with PWS treated with GH through childhood are able to achieve their expected midparental height (9). Recent studies have found that up to 72% of children with PWS treated with GH therapy have a serum IGF-I level that is greater than 2 SD values after 24 months of treatment, despite lower doses of GH than are used for children with isolated GH deficiency (15). However, IGF-I to IGF binding protein-3 ratios remained stable with GH therapy, suggesting that bioavailable IGF-I is not elevated to a greater extent than is seen in individuals with other causes of GH deficiency.

GH deficiency is also seen in 50% or more of adults with PWS (16). One study found that adults with PWS due to maternal uniparental disomy had lower GH secretion than those with deletion (17). Several studies have documented the safety and efficacy of GH treatment in adults with PWS on body composition and quality of life (18–21). One study found that the beneficial effects of GH therapy were unrelated to the pretreatment GH or serum IGF-I levels (20).

Although there have been concerns about an increased risk of death in children with PWS treated with GH therapy (22, 23), several studies have found that the rate of death in affected individuals on and off GH did not differ (24). A study of the natural history of PWS in one region of the United Kingdom found the overall death rate of individuals with PWS to be as high as 3% per year without GH therapy (25). Thus, the relationship of GH administration to unexpected death remains unclear, and parents need to be counseled about the potential risk before starting therapy. However, studies indicate that the benefits of treatment exceed the risks (26, 27).

Scoliosis is relatively common in children with PWS (40–80%), prompting concern about whether GH treatment would increase the frequency or severity of this finding. However, randomized trials have found no relationship between GH therapy and the age of onset or severity of scoliosis in children with PWS (28, 29).

Hypogonadism

Hypogonadism is present in both sexes and manifests as genital hypoplasia, incomplete pubertal development, and infertility in the vast majority. Genital hypoplasia is evident at birth (1–3). In males, the penis may be small and the scrotum is hypoplastic, poorly rugated, and poorly pigmented. Unilateral or bilateral cryptorchidism is present in 80–90% of males (1–3). In females, the genital hypoplasia is often overlooked; however, the clitoris and labia, especially the labia minora, are generally small from birth (1–3). The hypogonadism causes incomplete, delayed, and sometimes disordered pubertal development. Precocious adrenarche occurs in approximately 15–20% of cases in both sexes. Females have amenorrhea or oligomenorrhea. Infertility is the rule in both sexes, although a few instances of reproduction in females have been reported (30, 31). The largest recent study of hypogonadism, which included 84 individuals with PWS (half males, half females) ages 2–35 yr (32), identified the following frequencies in males: cryptorchidism, 100%; small testes, 76%; scrotal hypoplasia, 69%; in females: labia minora and/or clitoral hypoplasia, 76%; primary amenorrhea, 56%; spontaneous menarche (mostly spotting), 44% of those over age 15 yr; and in both sexes: premature pubarche, 14%; and precocious puberty, 3.6% (one male, two females). The hypogonadism in PWS is due to a combination of hypothalamic and primary gonadal deficiencies (33). Treatment with human chorionic gonadotropin is recommended as a treatment for infant males with undescended testes because it may help with testicular descent more than in typical males with cryptorchidism and also helps improve the size of the scrotal sac if orchidopexy is necessary in the future (8).

Central adrenal insufficiency (CAI)

In 2008, one study reported that CAI after overnight single-dose metyrapone tests was noted in 60% of children with PWS, suggesting that this may be the cause of the high incidence of sudden death in this population (34). It is known that introducing GH therapy can precipitate adrenal crisis in individuals with incipient adrenal insufficiency by accelerating the peripheral metabolism of cortisol, which may explain the correlation between the incidence of sudden death at the beginning of GH treatment and CAI in individuals with PWS (34). However, two subsequent studies have found normal cortisol responses to both low- and high-dose synacthen testing and insulin tolerance testing (35, 36), so whether CAI is a true issue for individuals with PWS remains uncertain. Patients should be counseled about symptoms consistent with adrenal insufficiency and educated about the best course of action and treatment should these symptoms occur.

Hypothyroidism

Central hypothyroidism, with a normal or low TSH value and low free T_4 level, has been documented in up to 25% of individuals with PWS, with a mean age of diagnosis and treatment of 2 yr (37–39).

Impaired glucose tolerance and diabetes mellitus

Up to 25% of adults with PWS (particularly those with significant obesity) have type 2 diabetes mellitus (40) with a mean age of onset of 20 yr. A study of a large French cohort with PWS (ages 2–18.8 yr) revealed the presence of impaired glucose tolerance in 4% of individuals (mean

age, 10.2 yr) but no diabetes mellitus in those less than 20 yr of age (41).

Additional Medical Issues

Obesity

Obesity in PWS typically precedes the hyperphagia and results from decreased total caloric requirement, due to decreased resting energy expenditure from decreased activity and decreased lean body mass (primarily muscle) compared with unaffected individuals (1–3). The obesity in PWS is primarily central (abdomen, buttocks, and thighs) in both sexes, and interestingly, there is less visceral fat in obese individuals than would be expected for the degree of obesity (42). Obesity and its complications are the major causes of morbidity and mortality in individuals with PWS.

The hyperphagia that occurs in PWS is believed to be caused by a hypothalamic abnormality resulting in lack of satiety. Several independent groups have shown that ghrelin levels are significantly elevated in hyperphagic older children and adults with PWS before and after meals (43–45). However, studies of infants with PWS have also shown that infants who are not interested in eating still have elevated levels of ghrelin. Thus, hyperghrelinemia precedes the development of obesity and increased appetite in PWS (46). However, several groups have now shown that pharmacological reduction of ghrelin to normal levels in PWS, using either short- or long-acting agents, did not affect the weight, appetite, or eating behavior in hyperphagic individuals (47, 48). Thus, there are no consistently identified hormonal abnormalities to explain the hyperphagia, and the metabolic correlates of hyperphagia in PWS are still uncertain.

Although early counseling, caloric restriction, and dietary recommendations have not changed the tempo or timing of the nutritional phases, it is possible to keep the weight for height normal before the child enters nutritional phase 2b. Retrospective review of growth charts of older individuals with PWS who were typically not diagnosed until 8–12 yr of age showed that they were already obese when they entered phase 2b, so the increased interest in food served to worsen their existing obesity (5). Additionally, parents of children diagnosed in infancy have the opportunity to institute food-related behavioral modification well before the child's appetite or interest in food increases. This allows them to proactively teach the child about healthy eating and food choices, as well as portion size, so that when phase 3 begins it is often less severe than what is described in the literature. However, a restrictive food environment is highly recommended when individuals with PWS enter nutritional phases 2b to 3, with food storage being locked, access to food or money to buy food being forbidden, and constant supervision being employed whenever possible.

Sleep abnormalities

Sleep abnormalities are well documented and include reduced rapid eye movement (REM) latency, altered sleep architecture, oxygen desaturation, and both central and obstructive apnea (49–52). Sleep studies are recommended before starting GH therapy and approximately 6–12 wk after beginning the therapy to ensure that GH is not worsening sleep abnormalities due to tonsillar/adenoid hypertrophy. Recommendations are for evaluation by an otolaryngologist and pulmonologist for consideration of tonsillectomy/adenoidectomy *vs.* continuous positive pressure if obstructive sleep apnea worsens with GH treatment (53). Primary hypothalamic dysfunction is thought to be the cause of the alterations in sleep microstructure and abnormalities in ventilation during sleep, with studies showing low levels of orexin and hypocretin in the cerebrospinal fluid and decreased levels of acetylcholinergic neurons in the pedunculopontine tegmental nucleus (54, 55). Some individuals with PWS have excessive daytime sleepiness, and some have symptoms of narcolepsy and/or cataplexy with rapid onset of REM sleep and decrease in non-REM sleep instability (55). Interestingly, the narcoleptic symptoms most often occur during eating in younger children with PWS. Modafinil has been found to be a safe and effective treatment for children with PWS with excessive daytime sleepiness, regardless of the etiology (56).

Behavioral issues

A characteristic behavior profile with temper tantrums, stubbornness, controlling and manipulative behavior, compulsivity, and difficulty with change in routine becomes evident in early childhood for many individuals with PWS. Some of the behavioral characteristics are suggestive of autism. Attention deficit/hyperactivity symptoms and insistence on sameness are common and typically of early onset (57). Self-mutilatory behaviors such as severe compulsive nail biting and/or skin-picking are common in individuals with PWS and anecdotally are thought to be associated with the increased appetite.

Approach to Our Patient

Our patient received feedings via a combination of oral and nasogastric tube once the diagnosis was established because it was known that his feeding pattern would improve relatively quickly. A course of human chorionic go-

nadotropin was given twice a week for 5 wk, and a sleep study was performed before hospital discharge. The child was sent to an endocrinologist for further treatment. GH therapy was begun, and the parents noted improvements in strength, daytime alertness, and eating. Occupational, physical, and speech therapies were started, and the patient was seen regularly by a dietician to ensure that the diet was optimized and that weight gain was adequate but not too rapid.

Existing Controversies

Controversies exist about the optimal age to begin GH therapy because, although the benefits of starting GH in children with PWS are clear, more and more evidence suggests that there may be even greater benefit to beginning treatment in infancy as opposed to waiting until the child is older. With parent support groups and internet access, parents are aware of the potential benefits of starting GH treatment in infancy, and many are requesting this therapy as soon as the diagnosis is made. Therefore, endocrinologists need to be cognizant of the data indicating the benefits of early GH treatment in this population. There is also debate as to the benefit of monitoring IGF-I levels for treatment optimization, given the fact that most individuals with PWS have elevated IGF-I levels 2 yr after initiation of treatment despite relatively low dosing. There is no consensus among endocrinologists about how best to handle the elevated IGF-I levels. Additionally, some endocrinologists doubt that CAI is a significant problem for those with PWS, whereas others insist that it is the cause of the high rate of sudden death. Questions remain about whether testing for CAI should be performed for all individuals with PWS or just those with symptoms of adrenal insufficiency. Additional controversy centers around treatment for hypogonadism and whether sex steroid treatment should be used for individuals with PWS and at what age treatment should be initiated.

Areas of Uncertainty

Many areas of uncertainty merit further discussion and research evaluation. First and foremost remains the issue of which hormones cause the changes in weight and appetite and how these could best be modified to reverse the obesity and hyperphagia. Additional areas of research include the determination of the optimal age at which to begin GH therapy and whether or not all adults with PWS should receive GH treatment, despite deficiency only being present in approximately 50%. The questions surrounding CAI and treatment for hypogonadism also deserve research evaluation. The relationship of behavioral problems, self-mutilatory behaviors, and sleep disturbances to appetite and obesity need to be identified, as well as better treatment options for these problems.

Conclusion

PWS is a complex disorder involving the hypothalamic-pituitary axis, resulting in a myriad of issues for the affected individual, including multiple endocrinopathies, obesity, sleep disorders, and behavioral problems. Research is being done to try to ameliorate many of these problems for individuals with PWS, but at this time early diagnosis, therapies, and treatment with GH have had positive effects for the younger generation with this syndrome. Proactive counseling about the various nutritional phases has helped parents work to prevent the early-onset obesity that has long been considered part of PWS. Parents of children with PWS can be optimistic about the future for their children in light of the improved knowledge and treatment options available.

Resources for Families

Prader-Willi Syndrome Association, 8588 Potter Park Drive, Suite 500, Sarasota, Florida 34238. Telephone: 800-926-4797 or 941-312-0400; fax: 941-312-0142. Web site: www.pwsausa.org.

Foundation for Prader-Willi Research, 104 Hume Avenue, Alexandria, Virginia 22301. Telephone: 703-683-7500; fax: 703-836-0959. Web site: www.fpwr.org.

Foundation for Prader-Willi Research Canada, 19-13085 Yonge Street, Suite 370, Richmond Hill, Ontario, Canada L4E 0K2. Telephone: 866-993-7972. Web site: www.onesmallstep.ca.

Acknowledgments

Much gratitude is expressed to Dr. Arlan Rosenbloom and Dr. Janet Silverstein, for their review and editing of this article, and to Dr. Daniel Driscoll for his mentoring.

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Funding was provided by the Lawson Wilkins Pediatric Endocrine Society, National Institutes of Health Grants 1K23 DK081203 and 1U54 RR019478, and General Clinical Research Center Grant M01 RR00082 from the National Center for Research Resources (to the University of Florida).

Disclosure Summary: The author has nothing to disclose.

References

1. **Glenn CC, Driscoll DJ, Yang TP, Nicholls RD** 1997 Genomic imprinting: potential function and mechanisms revealed by the Prader-Willi and Angelman syndromes. Mol Hum Reprod 3:321–332
2. **Bittel DC, Butler MG** 2005 Prader-Willi syndrome: clinical genetics, cytogenetics and molecular biology. Expert Rev Mol Med 7:1–20
3. **Horsthemke B, Buiting K** 2008 Genomic imprinting and imprinting defects in humans. Adv Genet 61:225–246
4. **Horsthemke B** 2010 Mechanisms of imprint dysregulation. Am J Med Genet C Semin Med Genet 154C:321–328
5. **Miller JL, Lynn CH, Driscoll DC, Goldstone AP, Gold JA, Kimonis V, Dykens E, Butler MG, Shuster JJ, Driscoll DJ** 2011 Nutritional phases in Prader-Willi syndrome. Am J Med Genet A 155A:1040–1049
6. **Butler MG, Sturich J, Lee J, Myers SE, Whitman BY, Gold JA, Kimonis V, Scheimann A, Terrazas N, Driscoll DJ** 2011 Growth standards of infants with Prader-Willi syndrome. Pediatrics 127:687–695
7. **Miller JL, Lynn CH, Shuster J, Driscoll DJ** 2012 A reduced-calorie, well-balanced diet improves weight control in children with Prader-Willi syndrome. J Hum Nutr Diet, in press
8. **McCandless SE, and the Committee on Genetics** 2011 Health supervision for children with Prader-Willi syndrome. Pediatrics 127:195–204
9. **Angulo MA, Castro-Magana M, Lamerson M, Arguello R, Accacha S, Khan A** 2007 Final adult height in children with Prader-Willi syndrome with and without human growth hormone treatment. Am J Med Genet A 143A:1456–1461
10. **Siemensma EP, Tummers-de Lind van Wijngaarden RF, Festen DA, Troeman ZC, van Alfen-van der Velden AA, Otten BJ, Rotteveel J, Odink RJ, Bindels-de Heus GC, van Leeuwen M, Haring DA, Oostdijk W, Bocca G, Mieke Houdijk EC, van Trotsenburg AS, Hoorweg-Nijman JJ, van Wieringen H, Vreuls RC, Jira PE, Schroor EJ, van Pinxteren-Nagler E, Willem Pilon J, Lunshof LB, Hokken-Koelega AC** 2012 Beneficial effects of growth hormone treatment on cognition in children with Prader-Willi syndrome: a randomized controlled trial and longitudinal study. J Clin Endocrinol Metab 97:2307–2314
11. **Eiholzer U, l'Allemand D, Schlumpf M, Rousson V, Gasser T, Fusch C** 2004 Growth hormone and body composition in children younger than 2 years with Prader-Willi syndrome. J Pediatr 144:753–758
12. **Festen DA, de Lind van Wijngaarden R, van Eekelen M, Otten BJ, Wit JM, Duivenvoorden HJ, Hokken-Koelega AC** 2008 Randomized controlled GH trial: effects on anthropometry, body composition and body proportions in a large group of children with Prader-Willi syndrome. Clin Endocrinol (Oxf) 69:443–451
13. **Osório J** 2012 Growth and development: growth hormone therapy improves cognition in children with Prader-Willi syndrome. Nat Rev Endocrinol 8:382
14. **Puga González B, Ferrández Longás A, Oyarzábal M, Nosas R; Grupo Colaborativo Español** 2010 The effects of growth hormone deficiency and growth hormone replacement therapy on intellectual ability, personality and adjustment in children. Pediatr Endocrinol Rev 7:328–338
15. **Feigerlová E, Diene G, Oliver I, Gennero I, Salles JP, Arnaud C, Tauber M** 2010 Elevated insulin-like growth factor-I values in children with Prader-Willi syndrome compared with growth hormone (GH) deficiency children over two years of GH treatment. J Clin Endocrinol Metab 95:4600–4608
16. **Sanchez-Ortiga R, Klibanski A, Tritos NA** 2012 Effects of recombinant human growth hormone therapy in adults with Prader-Willi syndrome: a meta-analysis. Clin Endocrinol (Oxf) 77:86–93
17. **Grugni G, Giardino D, Crinò A, Malvestiti F, Ballarati L, Di Giorgio G, Marzullo P** 2011 Growth hormone secretion among adult patients with Prader-Willi syndrome due to different genetic subtypes. J Endocrinol Invest 34:493–497
18. **Sode-Carlsen R, Farholt S, Rabben KF, Bollerslev J, Schreiner T, Jurik AG, Frystyk J, Christiansen JS, Höybye C** 2011 Growth hormone treatment for two years is safe and effective in adults with Prader-Willi syndrome. Growth Horm IGF Res 21:185–190
19. **Mogul HR, Lee PD, Whitman BY, Zipf WB, Frey M, Myers S, Cahan M, Pinyerd B, Southren AL** 2008 Growth hormone treatment of adults with Prader-Willi syndrome and growth hormone deficiency improves lean body mass, fractional body fat, and serum triiodothyronine without glucose impairment: results from the US multi-center trial. J Clin Endocrinol Metab 93:1238–1245
20. **Sode-Carlsen R, Farholt S, Rabben KF, Bollerslev J, Schreiner T, Jurik AG, Christiansen JS, Höybye C** 2012 Growth hormone treatment in adults with Prader-Willi syndrome: the Scandinavian study. Endocrine 41:191–199
21. **van Nieuwpoort IC, Deijen JB, Curfs LM, Drent ML** 2011 The relationship between IGF-I concentration, cognitive function and quality of life in adults with Prader-Willi syndrome. Horm Behav 59:444–450
22. **Eiholzer U, Nordmann Y, L'Allemand D** 2002 Fatal outcome of sleep apnoea in PWS during the initial phase of growth hormone treatment. A case report. Horm Res 58(Suppl 3):24–26
23. **Bakker B, Maneatis T, Lippe B** 2007 Sudden death in Prader-Willi syndrome: brief review of five additional cases. Concerning the article by U. Eiholzer *et al*. Deaths in children with Prader-Willi syndrome. A contribution to the debate about the safety of growth hormone treatment in children with PWS (Horm Res 2005;63:33–39). Horm Res 67:203–204
24. **Tauber M, Diene G, Molinas C, Hébert M** 2008 Review of 64 cases of death in children with Prader-Willi syndrome (PWS). Am J Med Genet A 146:881–887
25. **Whittington JE, Holland AJ, 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
26. **Carrel AL, Myers SE, Whitman BY, Eickhoff J, Allen DB** 2010 Long-term growth hormone therapy changes the natural history of body composition and motor function in children with Prader-Willi syndrome. J Clin Endocrinol Metab 95:1131–1136
27. **Miller J, Silverstein J, Shuster J, Driscoll DJ, Wagner M** 2006 Short-term effects of growth hormone on sleep abnormalities in Prader-Willi syndrome. J Clin Endocrinol Metab 91:413–417
28. **de Lind van Wijngaarden RF, de Klerk LW, Festen DA, Duivenvoorden HJ, Otten BJ, Hokken-Koelega AC** 2009 Randomized controlled trial to investigate the effects of growth hormone treatment on scoliosis in children with Prader-Willi syndrome. J Clin Endocrinol Metab 94:1274–1280
29. **Diene G, de Gauzy JS, Tauber M** 2008 Is scoliosis an issue for giving growth hormone to children with Prader-Willi syndrome? Arch Dis Child 93:1004–1006
30. **Eldar-Geva T, Hirsch HJ, Benarroch F, Rubinstein O, Gross-Tsur V** 2010 Hypogonadism in females with Prader-Willi syndrome from infancy to adulthood: variable combinations of a primary gonadal defect and hypothalamic dysfunction. Eur J Endocrinol 162:377–384
31. **Eldar-Geva T, Hirsch HJ, Rabinowitz R, Benarroch F, Rubinstein O, Gross-Tsur V** 2009 Primary ovarian dysfunction contributes to the hypogonadism in women with Prader-Willi syndrome. Horm Res 72:153–159
32. **Crinò A, Schiaffini R, Ciampalini P, Spera S, Beccaria L, Benzi F, Bosio L, Corrias A, Gargantini L, Salvatoni A, Tonini G, Trifirò G, Livieri C** 2003 Genetic Obesity Study Group of Italian Society of Pediatric Endocrinology and Diabetology (SIEDP). Hypogonadism and pubertal development in Prader-Willi syndrome. Eur J Pediatr 162:327–333
33. **Hirsch HJ, Eldar-Geva T, Benarroch F, Rubinstein O, Gross-Tsur V** 2009 Primary testicular dysfunction is a major contributor to abnormal pubertal development in males with Prader-Willi syndrome. J Clin Endocrinol Metab 94:2262–2268
34. **de Lind van Wijngaarden RF, Otten BJ, Festen DA, Joosten KF, de**

Jong FH, Sweep FC, Hokken-Koelega AC 2008 High prevalence of central adrenal insufficiency in patients with Prader-Willi syndrome. J Clin Endocrinol Metab 93:1649–1654
35. **Nyunt O, Cotterill AM, Archbold SM, Wu JY, Leong GM, Verge CF, Crock PA, Ambler GR, Hofman P, Harris M** 2010 Normal cortisol response on low-dose synacthen (1 microg) test in children with Prader Willi syndrome. J Clin Endocrinol Metab 95:E464–E467
36. **Farholt S, Sode-Carlsen R, Christiansen JS, Østergaard JR, Høybye C** 2011 Normal cortisol response to high-dose synacthen and insulin tolerance test in children and adults with Prader-Willi syndrome. J Clin Endocrinol Metab 96:E173–E180
37. **Miller JL, Goldstone AP, Couch JA, Shuster J, He G, Driscoll DJ, Liu Y, Schmalfuss IM** 2008 Pituitary abnormalities in Prader-Willi syndrome and early onset morbid obesity. Am J Med Genet A 146A:570–577
38. **Vaiani E, Herzovich V, Chaler E, Chertkoff L, Rivarola MA, Torrado M, Belgorosky A** 2010 Thyroid axis dysfunction in patients with Prader-Willi syndrome during the first 2 years of life. Clin Endocrinol (Oxf) 73:546–550
39. **Festen DA, Visser TJ, Otten BJ, Wit JM, Duivenvoorden HJ, Hokken-Koelega AC** 2007 Thyroid hormone levels in children with Prader-Willi syndrome before and during growth hormone treatment. Clin Endocrinol (Oxf) 67:449–456
40. **Butler JV, Whittington JE, Holland AJ, Boer H, Clarke D, Webb T** 2002 Prevalence of, and risk factors for, physical ill-health in people with Prader-Willi syndrome: a population-based study. Dev Med Child Neurol 44:248–255
41. **Diene G, Mimoun E, Feigerlova E, Caula S, Molinas C, Grandjean H, Tauber M; French Reference Centre for PWS** 2010 Endocrine disorders in children with Prader-Willi syndrome— data from 142 children of the French database. Horm Res Paediatr 74:121–128
42. **Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M; speakers contributors at the Second Expert Meeting of the Comprehensive Care of Patients with PWS** 2008 Recommendations for the diagnosis and management of Prader-Willi syndrome. J Clin Endocrinol Metab 93:4183–4197
43. **Bizzarri C, Rigamonti AE, Luce A, Cappa M, Cella SG, Berini J, Sartorio A, Müller EE, Salvatoni A** 2010 Children with Prader-Willi syndrome exhibit more evident meal-induced responses in plasma ghrelin and peptide YY levels than obese and lean children. Eur J Endocrinol 162:499–505
44. **Cummings DE, Clement K, Purnell JQ, Vaisse C, Foster KE, Frayo RS, Schwartz MW, Basdevant A, Weigle DS** 2002 Elevated plasma ghrelin levels in Prader Willi syndrome. Nat Med 8:643–644
45. **Haqq AM, Farooqi IS, O'Rahilly S, Stadler DD, Rosenfeld RG, Pratt KL, LaFranchi SH, Purnell JQ** 2003 Serum ghrelin levels are inversely correlated with body mass index, age, and insulin concentrations in normal children and are markedly increased in Prader-Willi syndrome. J Clin Endocrinol Metab 88:174–178
46. **Feigerlová E, Diene G, Conte-Auriol F, Molinas C, Gennero I, Salles JP, Arnaud C, Tauber M** 2008 Hyperghrelinemia precedes obesity in Prader-Willi syndrome. J Clin Endocrinol Metab 93:2800–2805
47. **Tan TM, Vanderpump M, Khoo B, Patterson M, Ghatei MA, Goldstone AP** 2004 Somatostatin infusion lowers plasma ghrelin without reducing appetite in adults with Prader-Willi syndrome. J Clin Endocrinol Metab 89:4162–4165
48. **De Waele K, Ishkanian SL, Bogarin R, Miranda CA, Ghatei MA, Bloom SR, Pacaud D, Chanoine JP** 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 159:381–388
49. **Festen DA, de Weerd AW, van den Bossche RA, Joosten K, Hoeve H, Hokken-Koelega AC** 2006 Sleep-related breathing disorders in prepubertal children with Prader-Willi syndrome and effects of growth hormone treatment. J Clin Endocrinol Metab 91:4911–4915
50. **Priano L, Grugni G, Miscio G, Guastamacchia G, Toffolet L, Sartorio A, Mauro A** 2006 Sleep cycling alternating pattern (CAP) expression is associated with hypersomnia and GH secretory pattern in Prader-Willi syndrome. Sleep Med 7:627–633
51. **Maas AP, Sinnema M, Didden R, Maaskant MA, Smits MG, Schrander-Stumpel CT, Curfs LM** 2010 Sleep disturbances and behavioural problems in adults with Prader-Willi syndrome. J Intellect Disabil Res 54:906–917
52. **Williams K, Scheimann A, Sutton V, Hayslett E, Glaze DG** 2008 Sleepiness and sleep disordered breathing in Prader-Willi syndrome: relationship to genotype, growth hormone therapy, and body composition. J Clin Sleep Med 4:111–118
53. **DeMarcantonio MA, Darrow DH, Gyuricsko E, Derkay CS** 2010 Obstructive sleep disorders in Prader-Willi syndrome: the role of surgery and growth hormone. Int J Pediatr Otorhinolaryngol 74:1270–1272
54. **Dauvilliers Y, Baumann CR, Carlander B, Bischof M, Blatter T, Lecendreux M, Maly F, Besset A, Touchon J, Billiard M, Tafti M, Bassetti CL** 2003 CSF hypocretin-1 levels in narcolepsy, Kleine-Levin syndrome, and other hypersomnias and neurological conditions. J Neurol Neurosurg Psychiatry 74:1667–1673
55. **Nevsimalova S, Vankova J, Stepanova I, Seemanova E, Mignot E, Nishino S** 2005 Hypocretin deficiency in Prader-Willi syndrome. Eur J Neurol 12:70–72
56. **De Cock VC, Diene G, Molinas C, Masson VD, Kieffer I, Mimoun E, Tiberge M, Tauber M** 2011 Efficacy of modafinil on excessive daytime sleepiness in Prader-Willi syndrome. Am J Med Genet A 155A:1552–1557
57. **Hartley SL, Maclean Jr WE, Butler MG, Zarcone J, Thompson T** 2005 Maladaptive behaviors and risk factors among the genetic subtypes of Prader-Willi syndrome. Am J Med Genet A 136:140–145