

# Recommendations for the diagnosis and management of Prader-Willi syndrome

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Short title: Recommendations for PWS

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## **Abstract**

**Objective:** To provide recommendations for the diagnosis and management of Prader-Willi syndrome throughout the lifespan to guide clinical practice.

**Participants:** An open international multidisciplinary expert meeting was held in October 2006 in Toulouse, France with 37 invited speakers and session chairs (see acknowledgements), and 85 additional registered participants. The meeting was supported by an unrestricted educational grant from Pfizer.

**Evidence:** Invited participants with particular expertise reviewed the published evidence-base for their specialist topic, and unpublished data from personal experience, previous National and International PWS Conferences and PWS Association Clinical Advisory Groups. Sessions covered Epidemiology, Psychiatric and Behavioural Disorders, Breathing and Sleep Abnormalities, Genetics, Endocrinology, and Management in Infancy, Childhood, Transition and Adulthood.

**Consensus Process:** Group meetings including open discussion after each session. The guidelines were written by the Scientific Committee (authors), using the conclusions provided by the sessions chairs and summary provided by each speaker, including incorporation of changes suggested after review by selected meeting participants (see acknowledgements).

**Conclusions:** The diagnosis and management of this complex disorder requires a multidisciplinary approach with particular emphasis on the importance of early diagnosis using accredited genetic testing, use and monitoring of GH therapy from early childhood, control of the food environment and regular exercise, appropriate management of transition, consideration of group home placement in adulthood and distinction of behavioural problems from psychiatric illness.

### **Introduction**

Prader-Willi syndrome (PWS) is a complex multi-system genetic disorder that arises from lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13 (1-5). The syndrome has characteristic phenotypes (6,7) including severe neonatal hypotonia, early onset of hyperphagia and development of morbid obesity, short stature, hypogonadism, learning disabilities, behavioural problems and psychiatric phenotypes with severe consequences and difficult management issues for patients, families and carers (6-10). While earlier prevalence estimates in the USA were in the range of 1 in 8,000 to 20,000, recent epidemiological surveys in Europe and Australia have estimated the lower limit of birth incidence at around 1 in 30,000, and population prevalence at about 1 in 50,000 (5,11-13). Recent surveys have highlighted the high rates and varied causes of morbidity and mortality throughout the natural history of the disease (14-16). There is a clear need for an integrated multidisciplinary approach to facilitate early diagnosis and optimise management to improve quality of life, prevent complications and prolong life-expectancy (17).

As the outcome of the recent expert meeting on the comprehensive care of patients with PWS, this paper summarises clinical practice guidelines, with emphasis on medical and behavioral/psychiatric management, adding to earlier publications also based on accumulated expert opinion (18,19). Due to space limitations, discussion about education, employment, social and sexual issues in the management of children and adults with PWS is out of the scope of these current recommendations. Readers are referred to other sources (19).

### **Diagnostic issues**

Although the diagnosis can easily be suspected from well defined clinical diagnostic criteria, even in the neonatal period, the increasing availability and application of molecular techniques means that genetic testing by an appropriately licensed laboratory is mandatory to confirm the diagnosis.

Over the last ten years, the age of diagnosis has fallen significantly and the majority of cases are now diagnosed during the first months of life (17,20,21). This should allow the earlier introduction of therapies to reduce the morbidity in particular by preventing obesity. This will not only increase the quality of life for patients but also reduce the burden on the family and carers.

### **Definition**

PWS arises from the lack of expression of genes on the paternally derived chromosome 15q11-q13. Candidate genes for PWS in this region are physiologically imprinted and silenced on the maternally inherited chromosome (4,10). PWS develops if the paternal alleles are defective, missing or silenced. In 75% of cases, there is paternal deletion of chromosome 15q11-q13 (type I or type II, depending on the proximal breakpoint) (22,23), maternal uniparental disomy (UPD) in 24%, imprinting errors in 1% (due in 15% of cases to either a sporadic or inherited microdeletion in the imprinting centre (for review see 24)), while there is a paternal chromosomal translocation in <1% of cases.

### **Genetic testing methods**

There are different methods for confirming the diagnosis and identifying the genetic subtype using peripheral blood lymphocytes (25). Since imprinted genes demonstrate differential DNA methylation dependent upon parental origin (3, 26) patients with PWS have a maternal-only imprint since they are lacking a paternal contribution. DNA methylation analysis is the only technique which can both confirm and reject the diagnosis of PWS and therefore should typically be the initial investigation of choice. This is most commonly done using DNA methylation-specific techniques at the *SNURF-SNRPN* locus (27-29). Parental samples are not required for this analysis. If DNA methylation analysis shows only a maternal pattern, then PWS is confirmed. Further methods may then be performed to determine the genetic subtype and to allow appropriate genetic counselling, in particular the recurrence risk.

Fluorescence *in-situ* hybridisation (FISH) analysis has the advantage of needing only a

sample from the proband to detect chromosome 15q11-q13 deletions in PWS (30). High-resolution chromosome analysis will only detect 60% of interstitial chromosome deletions (30). Chromosomal translocations or rearrangements may also be detected using this method. Negative FISH or karyotype analysis does not exclude the diagnosis and so if done first should be followed by DNA methylation analysis. Furthermore Angelman syndrome can present with neonatal hypotonia and FISH alone may therefore result in misdiagnosis, since it will detect maternal 15q11-q13 deletions.

If subsequent DNA methylation analysis is positive for PWS then DNA polymorphism analysis should be performed on the proband and parents to distinguish a maternal UPD from an imprinting defect (26,31). Patients with an imprinting defect (ID) warrant further investigation in a specialized lab to determine if an imprinting centre deletion is present (32,33). Those families with a child with an imprinting centre deletion have a recurrence risk of up to 50% if the father of the child is a carrier for the imprinting centre deletion (32, 33). The risk of recurrence in case of chromosomal translocations is evaluated up to 10%. In the other groups the risk of recurrence is the same as the general population.

In the future the new method, methylation specific multiplex ligation PCR amplification (MS-MLPA) may be more widely used as it has the advantage of combining dosing and DNA methylation analysis in one assay thus distinguishing PWS deletions from UPDs and IDs, as well as providing an approximate size of the deletion (34).

### **Genotype-phenotype correlations**

There are also several bi-allelic and maternally expressed, paternally imprinted genes throughout the PWS chromosomal region. Their relative under- or over-expression may explain the increasingly recognised genotype-phenotype correlations, such as differences between type I and II deletions, and between deletion and UPD. In particular hypopigmentation is seen primarily in those with deletion. Patients with UPD have less consistent presence of the characteristic facial phenotype and an increased risk of psychosis (35,36), but higher verbal intelligence scores

and less maladaptive behaviours (37-40), compared to patients with deletions. Intellectual ability, academic achievement, behavioural and psychological problems appear to be worse in subjects with the larger type I deletion than in type II deletion or UPD (41-45). More work will be needed before we can consider whether and how to translate these differences to individualise the management of patients according to their genotype.

### **Prenatal diagnosis**

A prenatal diagnosis is rarely made but theoretically it could be suspected in cases of reduced foetal movement and polyhydramnios (46). Genetic testing on samples obtained from chorionic villous sampling (CVS) and amniocentesis can be performed (47). FISH analysis can easily pick up deletions from such tissue, but DNA methylation analysis would be necessary for cases of UPD and IDs. However, the few clinical laboratories doing DNA methylation analysis in a prenatal setting are reluctant to use such CVS samples due to the relevant hypomethylation of this tissue. In the future the introduction of techniques such as comparative array genomic hybridisation might be transferred to prenatal diagnosis of PWS due to deletions with resulting ethical implications.

### **Postnatal diagnosis**

There is a marked clinical variability throughout life. The evolving phenotype from birth to adulthood means that the clinical features that should lead to a suspicion of the diagnosis depend on the age of the patient (Table 1). A diagnosis of PWS is particularly helpful during the first months of life, and should be thought of in all infants with severe and unexplained hypotonia (48). In addition the presence of a thin upper lip, almond-shaped eyes, acromicria (short hands and feet) and genital hypoplasia adds to the clinical diagnosis which should be confirmed by genetic testing. During childhood, a genetic test for PWS should not be performed in every obese child with learning disabilities, but a reduced growth velocity, specific dysmorphic features and history of neonatal hypotonia are strong pointers to initiate testing. Finally genetic testing should also be considered in adolescents and adults with a less marked phenotype but behavioural and psychological

problems in addition to obesity and delayed or incomplete gonadal maturation. Of note, is the fact that the absence of any of the core features of the early phenotype: hypotonia, failure to thrive (FTT) and, in boys, undescended testes, has been found to be associated with negative genetics for PWS (49).

### **Differential diagnosis**

Patients with negative testing for PWS should be investigated for other chromosomal deletions and duplications, and possible monogenic defects that are associated with PWS or PWS-like features (50-54). Other genetic obesity syndromes, such as Bardet-Biedel (BBS) and fragile X syndrome, associated with cognitive impairment, can sometimes cause clinical confusion (55). In BBS, although visual impairment does not usually emerge until 6-8 years, other phenotypes such as polydactyly (2/3 cases), brachydactyly and high arched palate can assist in early diagnosis.

### **Management of infants**

#### **Tube feeding**

Historically many neonates and infants were tube fed for more than 2 months because of severe hypotonia and poor suckling resulting in FTT, defined as descent across the centiles of weight or body mass index (BMI). There is no consensus to date on the optimal feeding regimen, whether the use of tube feeding is mandatory or should be used only after intensive and persistent nursing has failed, given the theoretical possibility that it could worsen speech problems. Concerns about the potentially long-term deleterious metabolic and cardiovascular effects of excessive weight gain during the first two years of life in non-PWS infants prompt caution against overfeeding in PWS with FTT (56,57).

#### **Cryptorchidism**

Cryptorchidism is present in over 80% of boys from birth (58,59). As with non-PWS boys, orchidopexy should be performed ideally during the first or the second year particularly as there is evidence of both primary and central hypogonadism (58,59), and rare cases of testicular cancer have been reported in PWS (60). Scrotal hypoplasia and the development of obesity can make surgery difficult if delayed

until a later age and could require repeated surgical interventions.

#### **Motor programme**

Children with PWS have muscular hypotonia, decreased muscle mass, psychomotor delay, and reduced motor activity (61), while increased variability in the size of both type I and II muscle fibres, and atrophy of activity-dependent type II fibres has been seen on biopsy (62). Training programs, initiated and supervised by physiotherapists and maintained by parents, have been used for many years without any evidence base (e.g. earlier onset of walking) but would seem sensible particularly in combination with GH treatment (see section below). Specific programs may be necessary to counteract the inability of the hypotonic PWS infant to overcome gravity while moving during the early years of life. These years may be a particularly sensitive period for motor development and skill acquisition which have consequences for cognitive and social development. Although hypotonia improves with age it does persist into adulthood together with reduced muscle mass and so exercise should be a regular part of daily life.

Speech and language therapy are also important during childhood to help with the impaired articulation and delay in development milestones seen in language acquisition (63,64).

#### **Parental guidance**

Early diagnosis offers the opportunity for education of parents, families, caregivers and other healthcare professionals to receive and give social, psychological and educational support (17,18). In addition, support from patient and family associations is increasingly available around the world ([www.ipwso.org](http://www.ipwso.org)).

### **Management of hyperphagia, obesity and its complications**

PWS has been classically described as having two phases: 1) poor feeding and frequently FTT and 2) onset of hyperphagia leading to obesity (8,65). Phase 1 occurs from birth to early infancy when infants with PWS have central hypotonia, a poor ability to suck and often require tube feeding. Phase 2 is described as beginning between age 1 and 6 years, usually between 2 and 4 years (65). Recent

examination of the natural history suggests a more complex progression leading to four main nutritional phases with sub-phases in the first two (66). Not all PWS individuals necessarily go through all the phases and sub-phases, which may be further altered by the use of GH.

In the first phase, the infant is hypotonic and not obese. Sub-phase 1a consists of feeding difficulties with or without FTT. In sub-phase 1b, the infant is growing steadily along a growth curve, at a normal rate.

In the second phase, body weight starts to increase. This generally occurs between 18-36 months of age. In sub-phase 2a, the child's weight increases such that it crosses one, two or more weight percentiles without a significant increase in calorie intake or increased interest in food. In sub-phase 2b, the child increases its daily calorie intake and becomes overweight or obese, with an abnormally increased interest in food but the appetite is not insatiable and unrelenting as in phase 3.

The onset of phase 3 is quite variable appearing as early as 3 years of age or as late as 15 years. This is the classical phase that most people typically associate with PWS, with aggressive food-seeking and a markedly reduced satiety. PWS patients in phase 3 have delayed meal termination and require significantly greater calorie intake compared to those without PWS to result in loss of hunger. There is also an early return of hunger after the previous meal with early meal initiation (67). Given free access to food, patients will consume approximately three times that of control subjects (68). This occurs despite delayed gastric emptying (69). Abnormalities in the satiety response to food intake in several corticolimbic regions are supported by observations from recent functional neuroimaging studies (70-72).

In phase 4, an individual may still have an increased appetite, but it is not as aggressive and unrelenting as previously observed, and seems to occur only in a subset of individuals in adulthood typically after 30 years of age.

Neuroanatomical abnormalities have been found in the post-mortem hypothalamus from

patients with PWS that may underlie the hyperphagia, particularly low oxytocin cell number (10), and structural brain defects are increasingly being recognised in imaging studies that may also contribute to cognitive and behavioural problems (73,74). In addition, fasting and post-prandial plasma levels of the orexigenic stomach-derived hormone ghrelin are greatly elevated in PWS, though do fall after food intake (75-79). Although somatostatin acutely suppresses plasma ghrelin concentrations in PWS patients, appetite is not reduced (80), while a recent study found no benefit of chronic administration of a long acting somatostatin analogue on weight or appetite in PWS (81). Furthermore levels of the anorexigenic gut hormone pancreatic polypeptide are reduced in PWS (10).

Obesity management involves environmental control with early institution of a low-calorie, well-balanced diet, with regular exercise, rigorous supervision, restriction of access to food and money with appreciation of legal and ethical obligations, appropriate psychological and behavioural counselling of the patient and family (82-84) (see later discussion under ethical issues). Early discussion with parents about the inevitability of hyperphagia, even during infancy, is essential for attempts to prevent obesity through their ability to set limits and the strict control of the food environment. This should be reemphasized at each visit.

Anecdotally, pharmacological treatment, including available anorexigenic agents, has not been of benefit in treating hyperphagia, though there are few published placebo-controlled studies (8,10,82,85). Study of any potential benefits of newer agents such as endocannabinoid antagonists are awaited in PWS, but recent concerns about psychiatric side effects will need careful monitoring in this group of patients. Restrictive bariatric surgery, such as gastric banding or bypass, have not been shown to reduce hyperphagia or achieve long-term weight reduction and are associated with unacceptable morbidity and mortality (for review see 86 and 87). While some of the reports using biliopancreatic diversion have reported successful weight loss, there were frequent complications from the resulting intestinal malabsorption (86,87). Importantly it is unknown whether changes in the food

environment might contribute to the outcomes following surgery.

Type 2 diabetes mellitus has been reported in around 25% of adults with PWS with a mean age of onset around 20 years (88). Although there is no data, it seems logical to approach diabetes management including weight loss and increased exercise, using similar pharmacological agents as with non-PWS obesity-related diabetes e.g. initially insulin sensitising agents, such as metformin or thiazolidinediones, with the introduction of insulin as required.

Body composition studies show both increased body fat and reduced muscle in PWS from infancy to adulthood (89-94). Interestingly magnetic resonance imaging has found a selective relative reduction in visceral adiposity in non-diabetic PWS adults of both sexes (95). This may explain the relative hypoinsulinaemia and normal triglyceride levels with preservation of insulin sensitivity and protective elevation in adiponectin levels in patients with PWS given their overall obesity (79,95-101). Use of lipid-lowering therapy may therefore be required less than might be expected. Hypertension may be present in up to 38% in adults (102), but is uncommon in children. There are no data on the advantages of particular drugs.

Physical activity in PWS is significantly reduced (103), related to obesity, hypersomnolence and persistent poor muscle tone. There is a reduced resting metabolic rate relative to body size, related to the abnormal body composition, which further contributes to a reduction in 24 hour energy expenditure (104,105). Increased physical activity and exercise programs are beneficial in improving body composition in PWS (106).

Deaths in PWS adults are most often obesity related due to cardiorespiratory failure, cor pulmonale exacerbated by obstructive and central apnoea, septicaemia due to skin infections, and pneumonia, and are seen from the teenage years into the 20s, 30s and beyond (16,21,107,108). Appropriate consultation with cardiologists and pneumologists in severely obese individuals is essential. Use of Continuous Positive Air Pressure (CPAP) and Nasal Intermittent Positive Pressure

Ventilation (NIPPV) may be beneficial but oxygen should be used cautiously because of the risk of hypoventilation with reversal of chronic hypoxia (109). Early introduction of graded exercise appears to be a vital part of cardiorespiratory rehabilitation (110).

Recent epidemiological surveys have also emphasized the risks of choking (8% of deaths) due to rapid consumption of food particularly in patients who are temporarily unsupervised (111), and gastric necrosis and rupture (2% of deaths) from overeating (13,112,113). The latter may be present despite the absence of usual clinical signs. Symptoms such as abdominal pain, vomiting or anorexia warrant detailed and rapid assessment with a low threshold for urgent imaging and surgical exploration.

### **Growth and GH treatment**

#### **Growth and GH status**

Mild prenatal growth retardation is common with median birth weight SDS of -1.37 (range -2.81 to +0.15), with 20% having SDS less than -2.0, and median birth length SDS of -0.46 SDS (range -2.14 to +1.40) (114). Both premature and post-term deliveries are frequently observed, with delivery more than 3 weeks early or late reported in some studies in around one third of cases each (46,115).

After birth, short stature is almost always present especially during the second year, because of GH insufficiency exacerbated by the lack of a pubertal growth spurt. In a large multinational cohort of 1135 children with PWS starting GH treatment, median height SDS was -2.2 SDS (-4.1 to -0.3) at a median age of 6.4 years (1.3 to 12.9) (115). The serum levels of IGF-I are reduced in the majority of children (116-119) and many adults (120,121). Spontaneous growth hormone secretion is reduced and GH peak during pharmacological stimulation test is less than 10 mcg/L in 70% of children (122). Adults with PWS have lower stimulated GH secretion than obese controls but the precise prevalence of severe GHD is unclear because reference ranges are unavailable in severe obesity (121,123). The experts agreed upon the potential importance of knowing the GH status in order to evaluate differential effects depending on GH status. In our experience, height velocity does not reflect

GH status in children with PWS particularly when they are obese. Therefore we agree that prior GH testing is not required before GH treatment but if available may be helpful. Mean spontaneous adult height has been reported as 162 cm in boys and 150 cm in girls (124) and 159 cm in boys and 149 cm in girls (125) in German cohorts.

### **GH treatment in children**

The aims of GH treatment in children with PWS are to improve growth during childhood, adult height and body composition (for review see 122). In randomized controlled studies using the currently recommended dose of 1.0 mg/m<sup>2</sup>/d, there is a significant increase in height, growth velocity and a decrease in percent body fat during the first year of GH treatment followed by stabilization during the second year. Lean body mass increased significantly during the first two years of GH treatment compared to untreated PWS children (126,127). After the initial 2 years, GH therapy for two additional years had continued beneficial effects on body composition when doses of 1.0 and 1.5 mg/m<sup>2</sup>/d were administered but not with a dose reduction to 0.3 mg/m<sup>2</sup>/d (126). This indicates that maintenance of improved body composition requires at least GH dose of 1.0 mg/m<sup>2</sup>/d. Bone mineral density continued to improve at all doses of GH. Only a few studies have reported data on adult height. In the KIGS database 33 patients (21 boys and 12 girls) reached adult height and 2/3 of them were above -2 SDS; the median adult height was -1 SDS for height after a mean duration of 8.4 years (114). In a recent report including 21 adults (13 boys, 8 girls), the mean adult height was -0.3 SDS for height after a mean duration of 7.9 yrs of GH treatment (128). Prior improvements in strength and agility that occurred during the initial 2 years were sustained, regardless of the GH dose. These improvements during GH treatment might contribute to the higher quality of life and reduced depression (129).

Hypothyroidism has been reported in children with PWS (130-133). It may be of central or peripheral origin requiring screening with TSH, free T4 and free T3 measurements prior to and on GH treatment. Replacement therapy is recommended if measurements dictate.

The benefits of starting GH treatment as early as 2 years are well established but there is increasing evidence of additional benefit in starting therapy between 6 and 12 months of age particularly in terms of motor development, muscle, head circumference and possibly cognition (94,134). Starting GH treatment early could be difficult in the USA where GH treatment is labelled for short stature. In Europe, growth retardation is not required in children with PWS for initiation of GH treatment.

Since October 2002, several reports of unexpected death in infants and children with PWS have been published (for review see 16). Most of them, whether in patients with or without GH treatment, were related to a complicated course of a relatively mild respiratory tract infection, sleep apnoea, adenoid and/or tonsil hypertrophy, hypoventilation and aspiration, or related to obesity. A recent review including 64 children (42 boys and 22 girls, 28 on GH treatment) suggested a high risk period of death during the 9 first months of GH treatment (16). For this reason it has been advised that GH treatment should be started at a low dose, such as 0.25 to 0.30 mg/m<sup>2</sup>/d or 0.009 to 0.012 mg/kg/day, increasing during the first weeks and months to reach a standard replacement GH dosage of around 1.0 mg/m<sup>2</sup>/d or 0.035 mg/kg/day, monitoring clinical effects particularly sleep apnoea (Table 2), and avoiding high IGF-I levels particularly if there is a clinical suspicion of over-treatment (oedema, worsening or new development of snoring, headache, acromegalic clinical features).

### **Sleep related breathing disorders**

A variety of sleep-related breathing disorders (SRBD) has been reported in PWS. Obstructive sleep apnoea syndrome (OSAS) may be caused by obesity, sticky saliva, kyphoscoliosis or adenotonsillar hypertrophy in combination with the narrow upper airways in PWS. Hypotonia of the respiratory muscles may also play a role. Recently, however, it has been demonstrated that non-obese pre-pubertal PWS children have mainly central sleep apnoea and only rarely OSAS during the night (135). The number of central apnoea/hypopnoea was increased (mean

number of 5/hour) and did not correlate with body mass index. Central sleep apnoea indicates a primary disturbance of the central respiratory control mechanism. When children with PWS are overweight, however, half of them have signs of OSAS (136). Arousal and cardiorespiratory responses to rapidly developing hypoxia and hypercapnia are also absent, decreased and/or delayed in PWS compared to control subjects of similar age, sex and BMI (137).

OSAS may lead to several complications, such as systemic hypertension, cardiovascular disease and cor pulmonale. Cor pulmonale plays an important role in the morbidity and mortality of patients with PWS. Rapid eye movement sleep abnormalities and excessive daytime sleepiness are common in PWS, and are considered a primary disorder. However, it cannot be excluded that sleep related breathing disorders disrupt sleep and induce excessive daytime sleepiness as is also found in the general population. In the general population, associations between SRBD and cognition, school performance, and psychiatric and behavioral co-morbidities are consistently reported. In individuals with PWS, OSAS is associated with behavioural disturbances, such as autistic related behaviour and impulsiveness (138). A recent study in young PWS infants found that OSAS was associated with lower mental development (139).

Five prospective studies have evaluated the effects of treatment with GH on breathing disorders in PWS (136,140-143). CO<sub>2</sub>-responsiveness, resting ventilation and airway occlusion pressure improved during 6-9 months of GH (140), and the inspiratory and expiratory muscle strength improved during 12 months of GH compared to controls (141). In a double-blind, placebo-controlled, cross-over study, a decrease in apnoea-hypopnoea index (AHI) was found after 6 months of GH in 12 PWS children, although the difference compared to controls was not statistically significant (142). Another study reported a decrease in AHI after 6 weeks of GH in most subjects of a mixed group of adults and children (143). A subset of patients had an increased AHI with more obstructive events after 6 weeks of GH, but most of these patients had upper respiratory tract infections and adenoid/tonsil hypertrophy during the second

evaluation and 2 among 6 had high IGF-I levels. Recently, a study in 35 pre-pubertal PWS children showed that the AHI did not significantly change during 6 months of GH therapy (135). However, four children had a marked increase in obstructive apnoeas during an upper respiratory disease. They continued with GH treatment, and when polysomnography was repeated after recovery, the obstructive apnoeas had disappeared. In light of these findings it is suggested that close attention be made to obesity, sleep and breathing problems both before and after commencement of GH treatment, with a low threshold for ear, nose and throat assessment and polysomnography (Table 2). Due to the high prevalence of sleep related breathing disorders, sleep studies and ENT evaluation should be performed whenever necessary in these children regardless of plans for GH treatment.

### **Orthopaedic treatment**

Scoliosis is a frequent feature observed in children with PWS with a prevalence of between 30 and 70 % (88,128,144-146). This high frequency may be explained partly by hypotonia and obesity. Unlike idiopathic scoliosis, young children are often affected with no gender bias. In a report of 139 children (mean age 10 years) the prevalence was 43%, and particularly high in young ages (15% before 5 years and 22% between 5 and 10 years) (146). Scoliosis is frequently associated with kyphosis particularly in obesity and both appear to be bad prognostic factors. Weight control is a vital part of its prevention and management. Due to the high frequency of scoliosis even in infants, spinal X-ray and, if appropriate orthopaedic assessment, are mandatory prior to GH treatment at any age. Regular clinical assessment is required at each visit, whether or not they are receiving GH. Reports of scoliosis worsening during GH treatment may simply reflect its natural history rather than a side effect of treatment in most cases. Cessation of GH is not justified in this situation.

Indications for bracing or surgery are the same as in idiopathic scoliosis. Surgical treatment is indicated in severe early-onset scoliosis-kyphosis and in adolescents near skeletal maturity. Complications are more frequent and

severe than in idiopathic scoliosis with a high risk of paraplegia (20%) and of major complications (30%, deep infections, pneumonia, hook out) (147-149). Surgical treatment requires a multidisciplinary team with expertise in the management of scoliosis associated with neuromuscular disease and PWS.

### **Induction of puberty**

Hypogonadism is a consistent feature in both males and females with PWS and hypogonadism is present even at birth. There is increasing evidence to implicate both central and peripheral origins for hypogonadism at least in males (59). Primate and testis specific gene expression has recently been discovered in the PWS chromosomal region (150,151). Surprisingly, minipuberty, described as gonadotrophin-dependant sex steroid secretion during the first months of life, seems to be present in males (152).

Most individuals will have no or delayed and incomplete puberty. Isolated premature pubarche (probably due to early maturation of zona reticularis of the adrenal gland) has been reported in 14% and precocious puberty in 4% of males and females (58,153,154). There is no consensus as to management of either of these conditions. Some investigators have suggested the use of hydrocortisone in premature pubarche to decrease adrenal androgens when there is associated advancement of bone age. Since early puberty is not usually sustained, treatment with GnRH analogs is not needed.

At some stage almost all subjects will require hormonal treatment for induction, promotion or maintenance of puberty. Mental retardation should not be a contraindication to allow normal pubertal development nor preclude sex hormone replacement at any age. Nevertheless management of hygiene issues in females whose menses are induced should be discussed with the family. There is no consensus as to the most appropriate regimen in PWS. This will be dictated by local availability and experience of different sex steroid preparations and some investigators have also supported the use of hCG (human chorionic gonadotropin) in boys (59,155). Whatever the chosen therapy, the dosing and timing should reflect as far as possible the process of normal puberty. The

prevalence of obesity in PWS provides further justification for the use of transdermal and non-synthetic oestrogen preparations which are usually well tolerated despite skin-picking. It remains to be seen whether concerns about aggressive behaviour during testosterone replacement are justified and could be better controlled with transdermal testosterone. However it would seem sensible to initiate and escalate therapy cautiously in boys. Initial low dose of intramuscular testosterone preparations (1/3 to 1/2 of the recommended dose for hypogonadal adults) with increments as tolerated should be considered when transdermal preparations are not tolerated.

### **Sex steroids replacement in adults**

Hypogonadism is a common but not necessarily universal finding in adults with PWS (58,59,121). Primary arguments for using sex steroid replacement in adults with PWS are known benefits to bone health, muscle mass metabolic protection and possible benefits to mental, emotional and physical well-being. Oestrogen levels in women with PWS may not be as low as post-menopausal levels perhaps related to aromatization of androgens from excess adipose tissue (95,156). Testosterone levels in men are often subnormal, though low sex hormone binding globulin levels (SHBG) related to obesity may mean that free testosterone levels are higher than total testosterone levels might indicate (95).

Patients with PWS have low bone mineral density (BMD) and are at risk of osteoporosis, related to deficiencies of sex steroids and GH, and low muscular activity, with elevated biochemical markers of bone turnover (89,121,156-159). Reduced BMD in PWS is associated with high risk of fracture in the long bones as well as in the small bones of the hands and feet, with some patients sustaining multiple fractures (88,148). These findings support the need for hormone therapy, particularly sex steroids replacement, during adolescence. However, neither standardized protocols for the prevention of osteoporosis nor systematic studies of sex hormones treatment in adolescents or adults with PWS are actually available. Oestrogen and androgen status should be monitored yearly during adolescence and adulthood and BMD assessed

as indicated by dual-energy X-ray photon absorptiometry (DEXA).

There are few case reports of pregnancy in females with PWS (160-162). Their cognitive dysfunction, social and emotional immaturity and the risk of Angelman syndrome in offspring of PWS deletion mothers, prompt us to advise against pregnancy. Sexual counselling and contraceptive treatment should be used as appropriate. In females with PWS, the use of gonadal hormone replacement should be considered if there is amenorrhoea/oligomenorrhoea or BMD becomes low-normal in the presence of reduced oestradiol levels (158). Administration of testosterone should be considered in men with PWS as for any other hypogonadal subject. Androgen therapy can be more physiologically administered using the new delivery systems of testosterone patches and gel preparations. This avoids the peaks and troughs of injections which may be of particular interest in PWS because of historical concerns about aggressive behavior with testosterone treatment. Although normal sperm development has been reported in some orchidectomy specimens, there are no reports of paternity in PWS (Vogels et al., oral communication, 6<sup>th</sup> International PWS Meeting, Cluj, Romania, 2007).

In conclusion, sex steroid therapy should be ideally minimized and titrated based on individual assessment, BMD, quality of life, sexual and psychosocial issues, acceptability of menstruation, and potential side effects.

### **Transition into adult life**

As with other chronic diseases and disabilities, adolescents with PWS struggle with the move from childhood to adulthood (163). New healthcare settings and providers, concerns about autonomy and the changing sexual, psychological, social and financial environment produce challenges particularly if disruption of comprehensive care is to be avoided. Furthermore, the behavioural and psychiatric problems and pervasive food seeking specific to PWS add an even higher level of complexity. Nevertheless health professionals, carers, patients and their families should be encouraged that the earlier diagnosis, multidisciplinary care and use of GH has had significant benefit in reducing

morbidity and altering the disease profile at adolescence. It is hoped that in the future, the prevalence of morbid and life threatening obesity at adolescence will continue to decrease from that seen in historical cohorts. Continuing these benefits into adulthood will require extension of comprehensive care to now involve adult endocrinologists in conjunction with paediatric colleagues, psychiatrists and medical doctors specialized in persons with intellectual disabilities.

The potential benefits of continuing, starting or re-starting GH treatment after completion of growth are achievement of a normal peak bone mass, continued improvement of muscle mass and strength, reduction of body fat, prevention of cardiovascular morbidity and improvement in well-being and quality of life (164). National circumstances often dictate cessation of GH treatment and re-evaluation of GH status at final height. Personal experience is that body composition can rapidly worsen upon stopping GH at that time emphasizing the need for formal GH cessation studies. Persistence of GH deficiency (70% partial, 38% severe) and low IGF-I have been reported in many adults with PWS (119,120).

Modest benefits in body composition, improved cognition, motor performance and social status have been reported with short term GH treatment of GH naïve PWS adults using the lower conventional GH dosage (0.53 mg/day) (120). However such studies may not reflect the outcomes of cessation studies at adolescence for example because of differences in baseline phenotype. Reports of other potential benefits of GH in either circumstance are awaited.

Utilization of transition clinics for chronic endocrine disease may be particularly helpful in the management of adolescents with PWS in this particular period, such as those developed for type1 diabetes mellitus, Turner syndrome, and childhood-onset GH deficiency.

### **Management of behaviour and psychiatric problems**

Before considering the treatment and management of behavioural and psychiatric problems in PWS it is important to consider what is known about such disorders, and

specifically the underlying biological and psychological mechanisms. Recent research suggests that the propensity to over-eating, repetitive and ritualistic behaviours and mood disorder may have different aetiologies and by implication respond to different treatment approaches and management strategies. The increased propensity to a pattern of behavioural and psychiatric problems that appears specific to PWS cannot be accounted for by some other non-specific factor such as the presence of intellectual disabilities (165-167). In addition to the universal presence of the propensity to over-eating, compulsive and ritualistic behaviours (82,168), a predisposition to temper outbursts (169) and skin picking are also very common although not universal. More recently studies of affective disorders and psychiatric illness in people with PWS has found that such disorders (including bipolar disorder) are common in PWS regardless of genetic sub-type but that prevalence rates of affective psychotic disorder are significantly greater in those with UPD (170). In the population-based study that first reported this (35), all 5 people with UPD 28 years or older had had a psychotic illness, while only one out of 9 with the deletion form of PWS had had a similar illness. Whilst affective disorder in general in PWS is characterised by various degrees of mood fluctuation which may vary from brief and rapid changes in mood to more prolonged changes in affective state, the psychotic illness is characterised by both auditory hallucinations and persecutory delusions.

#### **Management of temper outbursts, repetitive and ritualistic behaviours**

The increased propensity to these behaviours in people with PWS may be as a consequence of developmental arrest (167). The approach is one of management rather than treatment in that the interventions are primarily behavioural with the identification of those factors that predispose, precipitate, or maintain such behaviours. Interventions are then based on the strategies that minimises the occurrence of such behaviours and most effectively manages them when they do occur. Inconsistent approaches or managements strategies that positively reinforce the unwanted behaviours will only increase the chance that they will occur again in the future. Families and those with PWS therefore need support from

psychologists and other professionals to: a) identify those individual and environmental factors that are associated with an increased risk of or the occurrence of temper outbursts or repetitive behaviours; b) develop management strategies that are informed by these observations; and c) guide how such strategies can be implemented by family members and others in a consistent and acceptable manner.

#### **Management of affective disorder including affective psychosis**

The development of abnormal mood states results from a complex interaction between the biological predisposition and past and present environmental factors that add to such a predisposition and may precipitate its manifestation. Their presentation may not be immediately obvious. A deterioration in the pattern of existing behaviour or the onset of new problem behaviours may be markers for an underlying abnormal mood state. This eventually becomes apparent with evidence of fluctuating mood, suicidal thoughts, loss of interest, a deterioration in the ability to concentrate, change in sleep pattern, under or over activity, and/or abnormal mental beliefs or experiences. All of these may be of sufficient severity to impact on the person's functional abilities and quality of life. Management and treatment will critically depend both on the diagnosis or not of a mood disorder and on the understanding of the circumstances that have led to the problem developing. The interventions need to consider: a) factors in the immediate environment (e.g. high level of demand, changes in routine) that might have precipitated a change in mood state; b) the use of medication known to be effective in the treatment of mood disorders and/or psychotic illness; and c) any other factors that are potentially relevant, such as the effects of any additional medical illness, other phenotypes (e.g. sleep disorders), other medications and/or the impact of life events (such as bereavement) on his/her mental state. In terms of the use of medication, the precise medication or combination of medications that might be used will depend on the co-morbid diagnoses made. Where depression is severe then antidepressant medication may be indicated, and if psychotic symptoms are also present antipsychotic medication may also be required. There is only limited research available in PWS about the

benefits of psychiatric medications for the treatment of psychiatric illness in PWS but antidepressants and antipsychotic medication may be better than mood stabilising medication (171). However, further research is required. Such medications must be given with care, starting on lower than normal doses with careful monitoring for adverse events. Whilst medication can help to return a person to a normal mental state and reduce the risk of relapse it is also important to look to how a predictable, low stress environment can be maintained and, when the person is able to do so, how any particular issues that may be important in his/her life can be addressed (e.g., bereavement, relationships etc).

### **Skin picking**

Whilst research might indicate that the spectrum of behavioural problems observed in people with PWS have discrete aetiologies there are overlaps. The reason for skin picking in PWS is unclear but it has been proposed that it is associated with serotonergic dysfunction and mood. However, approaches to its management will include the use of distraction techniques or the use of activities that are incompatible with skin picking (e.g. activities using the hands) and/or medication to stabilise mood, as well as other established behavioural techniques. Topiramate has been reported to reduce skin-picking in one small open-label study (85). Infections or irritations from any skin lesion themselves will require treatment as such problems may aggravate the skin picking. Crucial to management is the identification of those environmental or individual factors that are associated with skin picking, for example, being unoccupied and bored, an abnormal mood state, or the presence of a pre-existing skin lesion.

### **Other issues**

**Eyes:** early screening and correction for myopia, hypermetropia or other eye problems is recommended. Strabismus is also frequent and may require surgery.

**Poor salivary production** is often observed which requires parents and child education. Products designed to increase saliva flow (special toothpaste, mouthwash and sugarless gum) are helpful. Individuals with PWS are less sensitive to thirst and are particularly at

risk of dehydration in warm temperatures. Education for regular daily drinking is necessary and could prevent dental complications.

**Teeth:** abnormal enamel and frequent caries have been previously reported but in a recent survey (172) PWS patients presented with a more favourable oral health status than those in previous studies. Orthodontic treatment is often needed and the timing of orthodontia can be complicated by the prolonged growth period.

### **Ethical issues**

The support of people who may be vulnerable, whether in childhood or adult life requires a careful balance between respecting individual wishes and autonomy, especially in adult life, on the one hand, and, on the other, protection from harm, exploitation or abuse. This is true for many people with intellectual disabilities. However, for people with PWS there are specific concerns predominately around the risks associated with over-eating and resultant obesity. How these are managed will substantially depend on the cultural context and on the laws of any given country.

In childhood once the diagnosis is made, and the parents have been helped to understand the particular problem of over-eating associated with the syndrome, there is a duty to act in their child's best interests. This will include managing the food environment and limiting access to food. Whilst this may not always be easy, particularly when the wishes of siblings have to be considered, controlling access to food outside the home environment (e.g. school) is even more problematic. This becomes even more difficult with increasing age and with greater levels of independence and, in adult life, there is a tension between respect for an adult's autonomy to make decisions for him/herself and the severe obesity that is likely to follow with all the health and social consequences.

There is no easy solution to this. However, the following need to be considered. First, those with PWS undoubtedly have an abnormality of satiety consequent upon their genetic abnormality. The result of this is that they have very limited control over their eating

behaviour. Secondly, the nature and severity of this likely abnormality of the feeding pathways is greater than that observed in those with normal obesity. Thirdly, the consequence of uncontrolled access to food is a level of obesity that results not only in very poor health (e.g. sleep and respiratory disorders, diabetes mellitus, severe oedema and cellulitis) but to restrictions on movement and a marked impairment on quality of life. Early death is likely. Fourthly, there is emerging evidence that people with PWS benefit from a 'food controlled' environment in ways that go beyond simply the prevention of obesity. When the food environment is controlled by others and mealtimes and snacks are carefully managed, people with PWS accept this and are then able to focus on different issues in their lives, other than just food.

The main task for families and for those providing support is to plan for the possibility of greater independence that comes with adult life and seek to establish support that balances respect for choice and autonomy but still controls access to food and limits and monitors the spending of money. Ideally these strategies have the agreement of the person with PWS and can then be justified on the grounds of consent and the fact that such an approach is clearly in the best interests of the person with PWS. The problems arise when someone, who is now an adult, refuses to agree to such a support package and to limitation on his/her access to food and/or money and decides he/she wants to live independently. In most countries it is for adults to make such decisions for themselves even if there are likely to be adverse consequences. Should the same general principle of respect for an adult's autonomy apply to people with PWS? One argument against such a view is that people with PWS lack the capacity to make choices about food. Through no fault of their own the majority of people with PWS do not have the ability to make judgements about when they have eaten enough and because they remain hungry, even after eating, they are unable to prevent themselves from continuing to eat. If this general principle is accepted then, it can be argued, that there is a duty of care and the task is to work with the person concerned to persuade them to accept living in an appropriately managed environment and if they refused to consider whether there are

lawful means whereby the person can be made to live in such an environment. Again anecdotal evidence is that, once living as such, people with PWS accept it and come to prefer living in a food controlled environment, even though they may resist such a course of action in the first instance.

### **Conclusion and future developments**

The complex genetics, aetiology, multiple phenotypes and evolving natural history of PWS means that a multi-disciplinary professional, parental, societal and environmental approach to the management is required with many challenges to reducing morbidity and mortality, and improving quality of life (Table 3). However over recent years, an increasing appreciation and availability of important management strategies have already made significant improvements in the life of those with PWS, e.g. early diagnosis, use of multi-disciplinary teams, introduction of GH treatment, control of the food environment and better understanding of the behavioural and psychiatric aspects (Table 4). While filling of the gaps in our understanding of the underlying science will translate and eventually guide clinical management of PWS (e.g. identification of genes and their link to particular phenotypes, genotype-phenotype correlations), several clinical and pathophysiological questions need to be urgently addressed to continue improvement in the care of patients with PWS (Table 5).

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## References

1. **Prader A, Labhart A, Willi H** 1956 Ein Syndrom von Adipositas, Kleinwuchs, Kryptorchismus und Oligophrenie nach myatonieartigem Zustand im Neugeborenenalter. *Schweiz Med Wochenschr* 6:1260-1261
2. **Nicholls RD, Knoll JH, Butler MG, Karam S, Lalande M** 1989 Genetic imprinting suggested by maternal heterodisomy in nondeletion Prader-Willi syndrome. *Nature* 342:281-285
3. **Driscoll DJ, Waters MF, Williams CA, Zori RT, Glenn CC, Avidano KM, Nicholls RD** 1992 A DNA methylation imprint, determined by the sex of the parent, distinguishes the Angelman and Prader-Willi syndromes. *Genomics* 13:917-924
4. **Nicholls RD, Knepper JL** 2001 Genome organization, function, and imprinting in Prader-Willi and Angelman syndromes. *Annu Rev Genomics Hum Genet* 2:153-175
5. **Cassidy SB** 1997 Prader-Willi syndrome *J Med Genet* 34:917-23
6. **Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitman BY, Greenberg F** 1993 Prader-Willi syndrome: consensus diagnostic criteria. *Pediatrics* 91:398-402
7. **Gunay-Aygun M, Schwartz S, Heeger S, O’Riordan MA, Cassidy SB** 2001 The changing purpose of Prader-Willi syndrome clinical diagnostic criteria and proposed revised criteria. *Pediatrics* 108:E92
8. **Dykens E, Shah B** 2003 Psychiatric disorders in Prader-Willi syndrome: epidemiology and management. *CNS Drugs* 17:167-178
9. **Bittel DC, Butler MG** 2005 Prader-Willi syndrome: clinical genetics, cytogenetics and molecular biology. *Expert Rev Mol Med* 25:1-20
10. **Goldstone AP** 2004 Prader-Willi syndrome: advances in genetics, pathophysiology and treatment. *Trends Endocrinol Metab* 15:12-20
11. **Vogels A, Van Den Ende J, Keymolen K, Mortier G, Devriendt K, Legius E, Fryns JP** 2004 Minimum prevalence, birth incidence and cause of death for Prader-Willi syndrome in Flanders. *Eur J Hum Genet* 12:238-240
12. **Thomson AK, Glasson EJ, Bittles AH** 2006A long-term population-based clinical and morbidity review of Prader-Willi syndrome in Western Australia. *J Intellect Disabil Res* 50:69-78
13. **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
14. **Schrander-Stumpel CT, Curfs LM, Sastrowijoto P, Cassidy SB, Schrander JJ, Fryns JP** 2004 Prader-Willi syndrome: causes of death in an international series of 27 cases. *Am J Med Genet A* 124:333-338
15. **Eiholzer U** 2005Deaths in children with Prader-Willi syndrome. A contribution to the debate about the safety of growth hormone treatment in children with PWS. *Horm Res* 63:33-39
16. **Tauber M, Diene G, Molinas C, Hébert M** 2008 A Review of 64 Cases of Death in Children with Prader-Willi Syndrome (PWS). *Am J Med Genet A* 46:881-887
17. **Bacheré N, Diene G, Delagnes V, Molinas C, Moulin P, Tauber M** 2008 Early diagnosis and multidisciplinary care reduce the hospitalisation time and duration of tube feeding and prevent early obesity in PWS infants. *Horm Res* 69:45-52
18. **Eiholzer U, l’Allemand D, Zipf WB** 2003 Prader-Willi syndrome as a model of obesity. Karger, Switzerland
19. **Butler MG, Lee PDK, Whitman BY** 2006 Management of Prader-Willi syndrome. 3<sup>rd</sup> ed. Springer, NY, USA.

20. **Diene G, Molinas C, Barat P, Colle M, Dallavalle F, Garnier P, Jeandel C, Jésuran-Pérelroizen M, Lienhardt A, Mas JC, Moncla A, Nicolino M, Puel O, Simonin G, Wagner K, Tauber M** 2006 The French reference centre of PWS patients: preliminary results of the children database Program of the 45th Annual Meeting of The European Society of Pediatric Endocrinology, Rotterdam, Netherlands, 2006, p 77
21. **McManus B, Heinemann J** 2006 PWSA (USA) database. The Gathered View, Nov-Dec
22. **Amos-Landgraf JM, Ji Y, Gottlieb W, Depinet T, Wandstrat AE, Cassidy SB, Driscoll DJ, Rogan PK, Schwartz S, Nicholls RD** 1999 Chromosome breakage in the Prader-Willi and Angelman syndromes involves recombination between large, transcribed repeats at proximal and distal breakpoints. *Am J Hum Genet* 65:370-386
23. **Chai JH, Locke DP, Grealley JM, Knoll JH, Ohta T, Dunai J, Yavor A, Eichler EE, Nicholls RD** 2003 Identification of four highly conserved genes between breakpoint hotspots BP1 and BP2 of the Prader-Willi/Angelman syndromes deletion region that have undergone evolutionary transposition mediated by flanking duplicons. *Am J Hum Genet* 73:898-925
24. **Horsthemke B, Buiting K** 2006 Imprinting defects on human chromosome 15. *Cytogenet Genome Res* 113:292-299
25. **American Society of Human Genetics/American College of Medical Genetics Test and Technology Transfer Committee** 1996 Diagnostic testing for Prader-Willi and Angelman Syndromes. *Am J Hum Genet* 58:1085-1088
26. **Glenn CC, Nicholls RD, Robinson WP, Saitoh S, Niikawa N, Schinzel A, Horsthemke B, Driscoll DJ** 1993 Modification of 15q11-q13 DNA methylation imprints in unique Angelman and Prader-Willi patients. *Hum Mol Genet* 2:1377-1382
27. **Glenn CC, Saitoh S, Jong MTC, Filbrandt MM, Surti U, Driscoll DJ, and Nicholls RD** 1996 Expression, DNA methylation, and gene structure of the human *SNRPN* gene. *Am J Hum Genet* 58:335-346
28. **Muralidhar B, Butler MG** 1998 Methylation PCR analysis of Prader-Willi syndrome, Angelman syndrome, and control subjects. *Am J Med Genet* 80:263-265.
29. **Chotai KA and Payne SJ** 1998 A rapid, PCR based test for differential molecular diagnosis of Prader-Willi and Angelman syndromes *J Med Genet* 35:472-475
30. **Butler MG** 1995 High resolution chromosome analysis and fluorescence in situ hybridization in patients referred for Prader-Willi or Angelman syndrome. *Am J Med Genet* 56:420-422
31. **Reis A, Dittrich B, Greger V, Buiting K, Lalonde M, Gillesen-Kaesbach G, Anvret M, Horsthemke B** 1994 Imprinting mutations suggested by abnormal DNA methylation patterns in familial Angelman and Prader-Willi syndromes. *Am J Hum Genet* 54:741-747
32. **Buiting K, Saitoh S, Gross S, Dittrich B, Schwartz S, Nicholls RD, Horsthemke B** 1995 Inherited microdeletions in the Angelman and Prader-Willi syndromes define an imprinting centre on human chromosome 15. Inherited microdeletions in the Angelman and Prader-Willi syndromes define an imprinting centre on human chromosome 15. *Nat Genet* 9:395-400
33. **Buiting K, Farber C, Kroisel P, Wagner K, Brueton L, Robertson ME, Lich C, Horsthemke B** 2000 Imprinting centre deletions in two PWS families: implications for diagnostic testing and genetic counseling. *Clin Genet* 58:284-290
34. **Procter M, Chou LS, Tang W, Jama M, Mao R** 2006 Molecular diagnosis of Prader-Willi and Angelman syndromes by methylation-specific melting analysis and methylation-specific multiplex ligation-dependent probe amplification. *Clin Chem* 52:1276-83

35. **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
36. **Vogels A, Matthijs G, Legius E, Devriendt K, Fryns JP** 2003 Chromosome 15 maternal uniparental disomy and psychosis in Prader-Willi syndrome. *J Med Genet* 40:72-73
37. **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
38. **Dykens EM, Cassidy SB, King BH** 1999 Maladaptive behavior differences in Prader-Willi syndrome due to paternal deletion versus maternal uniparental disomy. *Am J Ment Retard* 104:67-77
39. **Cassidy SB, Forsythe M, Heeger S, Nicholls RD, Schork N, Benn P, Schwartz S** 1997 Comparison of phenotype between patients with Prader-Willi syndrome due to deletion 15q and uniparental disomy 15. *Am J Med Genet* 68:433-440
40. **Veltman MW, Thompson RJ, Roberts SE, Thomas NS, Whittington J, Bolton PF** 2004 Prader-Willi syndrome--a study comparing deletion and uniparental disomy cases with reference to autism spectrum disorders. *Eur Child Adolesc Psychiatry* 13:42-50
41. **Butler MG, Bittel DC, Kibiryeveva N, Talebizadeh Z, Thompson T** 2004 Behavioral differences among subjects with Prader-Willi syndrome and type I or type II deletion and maternal disomy. *Pediatrics* 113:565-573
42. **Varela MC, Kok F, Setian N, Kim CA, Koiffmann CP** 2005 Impact of molecular mechanisms, including deletion size, on Prader-Willi syndrome phenotype: study of 75 patients. *Clin Genet* 67:47-52
43. **Milner KM, Craig EE, Thompson RJ, Veltman MW, Thomas NS, Roberts S, Bellamy M, Curran SR, Sporikou CM, Bolton PF** 2005 Prader-Willi syndrome: intellectual abilities and behavioural features by genetic subtype. *J Child Psychol Psychiatry* 46:1089-1096
44. **Hartley SL, Maclean WE Jr, 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
45. **Bittel DC, Kibiryeveva N, Butler MG** 2006 Expression of 4 genes between chromosome 15 breakpoints 1 and 2 and behavioral outcomes in Prader-Willi syndrome. *Pediatrics* 118:e1276-1283
46. **Whittington JE, Butler JV, Holland AJ** 2008 Pre-, peri- and postnatal complications in Prader-Willi syndrome in a UK sample. *Early Hum Dev* 84:331-336
47. **Glenn CC, Deng G, Michaelis RC, Tarleton J, Phelan MC, Surh L, Yang TP, Driscoll DJ** 2000 DNA methylation analysis with respect to prenatal diagnosis of the Angelman and Prader-Willi syndromes and imprinting. *Prenat Diagn.* 20:300-6
48. **Trifirò G, Livieri C, Bosio L, Gargantini L, Corrias A, Pozzan G, Crinò A; Genetic Obesity Study Group of the Italian Society of Paediatric Endocrinology and Diabetology** 2003 Neonatal hypotonia: don't forget the Prader-Willi syndrome. *Acta Paediatr* 92:1085-1089
49. **Whittington J, Holland A, Webb T, Butler J, Clarke D, Boer H** 2002 Relationship between clinical and genetic diagnosis of Prader-Willi syndrome. *J Med Genet* 39:926-932
50. **Gilhuis HJ, van Ravenswaaij CM, Hamel BJ, Gabreels FJ** 2000 Interstitial 6q deletion with a Prader-Willi-like phenotype: a new case and review of the literature. *Eur J Paediatr Neurol* 4:39-43

51. **D'Angelo CS, Da Paz JA, Kim CA, Bertola DR, Castro CI, Varela MC, Koiffmann CP** 2006 Prader-Willi-like phenotype: investigation of 1p36 deletion in 41 patients with delayed psychomotor development, hypotonia, obesity and/or hyperphagia, learning disabilities and behavioral problems. *Eur J Med Genet* 49:451-460
52. **Mitter D, Buiting K, von Eggeling F, Kuechler A, Liehr T, Mau-Holzmann UA, Prott EC, Wiczorek D, Gillessen-Kaesbach G** 2006 Is there a higher incidence of maternal uniparental disomy 14 [upd(14)mat]? Detection of 10 new patients by methylation-specific PCR. *Am J Med Genet A* 140:2039-2049
53. **Varela MC, Simoes-Sato AY, Kim CA, Bertola DR, De Castro CI, Koiffmann CP** 2006 A new case of interstitial 6q16.2 deletion in a patient with Prader-Willi-like phenotype and investigation of SIM1 gene deletion in 87 patients with syndromic obesity. *Eur J Med Genet* 49:298-305
54. **Yeo GS, Connie Hung CC, Rochford J, Keogh J, Gray J, Sivaramakrishnan S, O'Rahilly S, Farooqi IS** 2004 A de novo mutation affecting human TrkB associated with severe obesity and developmental delay. *Nat Neurosci* 7:1187-1189
55. **Goldstone AP, Beales PL** 2008 Genetic obesity syndromes. *Front Horm Res* 36:37-60
56. **Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB** 2000 Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ* 320967-971
57. **Stettler N, Zemel BS, Kumanyika S, Stallings VA** 2002 Infant weight gain and childhood overweight status in a multicenter, cohort study. *Pediatrics* 109:194-199
58. **Crino A, Schiaffini R, Ciampalini P, Spera S, Beccaria L, Benzi F, Bosio L, Corrias A, Gargantini L, Salvatoni A, Tonini G, Trifiro G, Livieri C; Genetic Obesity Study Group of Italian Society of Pediatric endocrinology and diabetology (SIEDP)** 2003 Hypogonadism and pubertal development in Prader-Willi syndrome. *Eur J Pediatr* 162:327-333
59. **Eiholzer U, l'Allemand D, Rousson V, Schlumpf M, Gasser T, Girard J, Gruters A, Simoni M** 2006 Hypothalamic and gonadal components of hypogonadism in boys with Prader-Labhart-Willi syndrome. *J Clin Endocrinol Metab* 91:892-898
60. **Jaffray B, Moore L, Dickson AP** 1999 Prader-Willi syndrome and intratubular germ cell neoplasia. *Med Pediatr Oncol* 32:73-74
61. **Goelz T** 2006 Motor and developmental interventions. In: Butler MG, Lee PDK, Whitman BY 2006 *Management of Prader-Willi syndrome*. 3rd ed. Springer, NY, USA, pp284-301.
62. **Sone S** 1994 Muscle histochemistry in the Prader-Willi syndrome. *Brain Dev.* 16:183-188.
63. **Defloor T, Van Borsel J, Curfs L** 2002 Articulation in Prader-Willi syndrome. *J Commun Disord* 35:261-282
64. **Lewis BA** 2006 Speech and language disorders associated with Prader-Willi syndrome. In: *Management of Prader-Willi syndrome*, eds. Butler MG, Lee PDK, Whitman BY. 3<sup>rd</sup> ed. Springer, NY USA; pp272-283
65. **Cassidy SB** 2001 Prader-Willi Syndrome. In: Cassidy SB, Allanson JE., eds *Management of Genetic Syndromes*. 1st ed. Wiley-Liss, New York;301-322
66. **McCune H, Driscoll DJ** 2005 Prader-Willi Syndrome. In: Efvall SW, Efvall VK eds. *Pediatric Nutrition in chronic diseases and developmental disorders*. 2nd edition. Oxford University Press, New York;128-132

67. **Holland AJ, 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 Relat Metab Disord* 17:527-532
68. **Zipf WB, Berntson GG** 1987 Characteristics of abnormal food-intake patterns in children with Prader-Willi syndrome and study of effects of naloxone. *Am J Clin Nutr* 46:277-281
69. **Choe YH, Jin DK, Kim SE, Song SY, Paik KH, Park HY, Oh YJ, Kim AH, Kim JS, Kim CW, Chu SH, Kwon EK, Lee KH** 2005 Hyperghrelinemia does not accelerate gastric emptying in Prader-Willi syndrome patients. *J Clin Endocrinol Metab* 90:3367-3370
70. **Hinton EC, Holland AJ, Gellatly MS, Soni S, Patterson M, Ghatei MA, Owen AM** 2006 Neural representations of hunger and satiety in Prader-Willi syndrome. *Int J Obes* 30:313-321
71. **Miller JL, James GA, Goldstone AP, Couch JA, He G, Driscoll DJ, Liu Y** 2007 Enhanced activation of reward mediating prefrontal regions in response to food stimuli in Prader-Willi syndrome. *J Neurol Neurosurg Psychiatry* 78:615-619
72. **Holsen LM, Zarcone JR, Brooks WM, Butler MG, Thompson TI, Ahluwalia JS, Nollen NL, Savage CR** 2006 Neural mechanisms underlying hyperphagia in Prader-Willi syndrome. *Obesity* 14:1028-1037
73. **Miller JL, Couch JA, Leonard CM, Schwenk K, Towler SD, Shuster J, Goldstone AP, He G, Driscoll DJ, Liu Y** 2007 Sylvian fissure morphology in Prader-Willi syndrome and early-onset morbid obesity. *Genet Med* 9:536-543
74. **Miller JL, Couch JA, Schmalfuss I, He G, Liu Y, Driscoll DJ** 2007 Intracranial abnormalities detected by three-dimensional magnetic resonance imaging in Prader-Willi syndrome. *Am J Med Genet A* 143:476-483
75. **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
76. **DelParigi A, Tschop M, Heiman ML, Salbe AD, Vozarova B, Sell SM, Bunt JC, Tataranni PA** 2002 High circulating ghrelin: a potential cause for hyperphagia and obesity in Prader-Willi syndrome. *J Clin Endocrinol Metab* 87:5461-5464
77. **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
78. **Tauber M, Conte Auriol F, Moulin P, Molinas C, Delagnes V, Salles JP** 2004 Hyperghrelinemia is a common feature of Prader-Willi syndrome and pituitary stalk interruption: a pathophysiological hypothesis. *Horm Res* 62:49-54
79. **Goldstone AP, Patterson M, Kalingag N, Ghatei MA, Brynes AE, Bloom SR, Grossman AB, Korbonits M** 2005 Fasting and postprandial hyperghrelinemia in Prader-Willi syndrome is partially explained by hypoinsulinemia, and is not due to peptide YY3-36 deficiency or seen in hypothalamic obesity due to craniopharyngioma. *J Clin Endocrinol Metab* 90:2681-2690
80. **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
81. **Waele K, Ishkanian S, Bogarin R, Miranda C, Ghatei M, Bloom S, 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*. (in press)

82. **Dykens EM, Leckman JF, Cassidy SB** 1996 Obsessions and compulsions in Prader-Willi syndrome. *J Child Psychol Psychiatry* 37:995-1002
83. **Holland AJ, Wong J** 1999 Genetically determined obesity in Prader-Willi syndrome: the ethics and legality of treatment. *J Med Ethics* 25:230-236
84. **Eiholzer U, Nordmann Y, l'Allemand D, Schlumpf M, Schmid S, Kromeyer-Hauschild K** 2003 Improving body composition and physical activity in Prader-Willi Syndrome. *J Pediatr* 142:73-78
85. **Shapira NA, Lessig MC, Lewis MH, Goodman WK, Driscoll DJ** 2004 Effects of topiramate in adults with Prader-Willi syndrome. *Am J Ment Retard* 109:301-309
86. **Papavramidis ST, Kotidis EV, Gamvros O** 2006 Prader-Willi syndrome-associated obesity treated by biliopancreatic diversion with duodenal switch. Case report and literature review. *J Pediatr Surg* 41:1153-1158
87. **Scheimann AO, Butler MG, Gourash L, Cuffari C, Klish W** 2008 Critical analysis of bariatric procedures in Prader-Willi syndrome. *J Pediatr Gastroenterol Nutr.* 46:80-3
88. **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
89. **Brambilla P, Bosio L, Manzoni P, Pietrobelli A, Beccaria L, Chiumello G** 1997 Peculiar body composition in patients with Prader-Labhart-Willi syndrome. *Am J Clin Nutr* 65:1369-1374
90. **Goldstone AP, Unmehopa UA, Bloom SR, Swaab DF** 2002 Hypothalamic NPY and agouti-related protein are increased in human illness but not in Prader-Willi syndrome and other obese subjects. *J Clin Endocrinol Metab* 87:927-937
91. **Eiholzer U, l'Allemand D, van der Sluis I, Steinert H, Gasser T, Ellis K** 2000 Body composition abnormalities in children with Prader-Willi syndrome and long-term effects of growth hormone therapy. *Horm Res* 53:200-206
92. **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
93. **Carrel AL, Myers SE, Whitman BY, Allen DB** 1999 Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome: A controlled study. *J Pediatr* 134:215-221
94. **Carrel AL, Moerchen V, Myers SE, Bekx MT, Whitman BY, Allen DB** 2004 Growth hormone improves mobility and body composition in infants and toddlers with Prader-Willi syndrome. *J Pediatr* 145:744-749
95. **Goldstone AP, Thomas EL, Brynes AE, Bell JD, Frost G, Saeed N, Hajnal JV, Howard JK, Holland A, Bloom SR** 2001 Visceral adipose tissue and metabolic complications of obesity are reduced in Prader-Willi syndrome female adults: evidence for novel influences on body fat distribution. *J Clin Endocrinol Metab* 86:4330-4338
96. **Tomita T, Greeley G Jr, Watt L, Doull V, Chance R** 1989 Protein meal-stimulated pancreatic polypeptide secretion in Prader-Willi syndrome of adults. *Pancreas* 4:395-400
97. **Schuster DP, Osei K, Zipf WB** 1996 Characterization of alterations in glucose and insulin metabolism in Prader-Willi subjects. *Metabolism* 45:1514-1520
98. **Mogul HR, Lee PD, Whitman B, Zipf W, Frey M, Myers SE, Cahan M, Pinyerd B** 2004 Preservation of insulin sensitivity and paucity of metabolic syndrome symptoms in Prader Willi syndrome adults: preliminary data from the US multi-center stud. *Obes Res* 12 :171 (Abstract)

99. **Hoybye C, Bruun JM, Richelsen B, Flyvbjerg A, Frystyk J** 2004 Serum adiponectin levels in adults with Prader-Willi syndrome are independent of anthropometrical parameters and do not change with GH treatment. *Eur J Endocrinol* 151:457-461
100. **Kennedy L, Bittel DC, Kibiryeveva N, Kalra SP, Torto R, Butler MG** 2006 Circulating adiponectin levels, body composition and obesity-related variables in Prader-Willi syndrome: comparison with obese subjects. *Int J Obes (Lond)* 30:382-387
101. **Festen DA, van Toorenenbergen A, Duivenvoorde HJ, Hokken-Koelega AC** 2007 Adiponectin levels in prepubertal children with Prader-Willi syndrome before and during growth hormone therapy. *J Clin Endocrinol Metab* 92:1549-1554
102. **Vogels A, Fryns JP** 2004 Age at diagnosis, body mass index and physical morbidity in children and adults with the Prader-Willi syndrome. *Genet Couns* 15:397-404
103. **van Mil EG, Westerterp KR, Kester AD, Curfs LM, Gerver WJ, Schrandt-Stumpel CT, Saris WH** 2000 Activity related energy expenditure in children and adolescents with Prader-Willi syndrome. *Int J Obes Relat Metab Disord* 24:429-434
104. **van Mil EA, Westerterp KR, Gerver WJ, Curfs LM, Schrandt-Stumpel CT, Kester AD, Saris WH** 2000 Energy expenditure at rest and during sleep in children with Prader-Willi syndrome is explained by body composition. *Am J Clin Nutr* 71:752-756
105. **A.P.Goldstone, A.E.Brynes, E.L.Thomas, J.D.Bell, G.Frost, A.Holland, M.A.Ghatei & S.R.Bloom** 2002 Resting metabolic rate, plasma leptin concentrations, leptin receptor expression, and adipose tissue measured by whole-body magnetic resonance imaging in women with Prader-Willi syndrome. *American Journal of Clinical Nutrition* 5:468-475
106. **Silverthorn KH, Hornak JE** 1993 Beneficial effects of exercise on aerobic capacity and body composition in adults with Prader-Willi syndrome. *Am J Ment Retard* 97:654-658
107. **Einfeld SL, Kavanagh SJ, Smith A, Evans EJ, Tonge BJ, Taffe J** 2006 Mortality in Prader-Willi syndrome. *Am J Ment Retard*. 111:193-198
108. **Grugni G, Crinò A, Bosio L, Corrias A, Cuttini M, De Toni T, Di Battista E, Franzese A, Gargantini L, Greggio N, Iughetti L, Livieri C, Naselli A, Pagano C, Pozzan G, Ragusa L, Salvatoni A, Trifirò G, Beccaria L, Bellizzi M, Bellone J, Brunani A, Cappa M, Caselli G, Cerioni V, Delvecchio M, Giardino D, Iannì F, Memo L, Pilotta A, Pomara C, Radetti G, Sacco M, Sanzari A, Sartorio A, Tonini G, Vettor R, Zaglia F, Chiumello G; Genetic Obesity Study Group of Italian Society of Pediatric Endocrinology and Diabetology (ISPED)** 2008 The Italian National Survey for Prader-Willi syndrome: an epidemiologic study. *Am J Med Genet A* 146:861-872.
109. **Nixon G, Brouillete R** 2002 Sleep and breathing in Prader Willi syndrome. *Pediatr Pulmonol* 34:209-217
110. **Gourash LM, Hanchett JE, Forster JL** 2006 Inpatient crisis intervention for persons with Prader-Willi syndrome. In: Butler MG, Lee PDK, Whitman BY, Eds. *Management of Prader-Willi syndrome*. 3rd ed. Springer, NY USA; 395-425
111. **Stevenson DA, Heinemann J, Angulo M, Butler MG, Loker J, Rupe N, Kendell P, Clericuzio CL, Scheimann AO** 2007 Deaths due to choking in Prader-Willi syndrome. *Am J Med Genet A* 143:484-487

112. **Wharton RH, Wang T, Graeme-Cook F, Briggs S, Cole RE** 1997 Acute idiopathic gastric dilation with gastric necrosis in individuals with Prader-Willi syndrome. *Am J Med Genet* 73:437-441
113. **Stevenson DA, Heinemann J, Angulo M, Butler MG, Loker J, Rupe N, Kendell P, Cassidy SB, Scheimann A** 2007 Gastric rupture and necrosis in Prader-Willi syndrome. *J Pediatr Gastroenterol Nutr* 45:272-274
114. **Tauber M** 2007 Effects of growth hormone treatment in children presenting with Prader-Willi syndrome: the KIGS experience. In: Ranke MB, Price DA, Reiter EO, Growth hormone therapy in Pediatrics–20 years of KIGS. Basel/Karger; 377-387
115. **Fridman C, Kok F, Koiffmann CP** 2000 Hypotonic infants and the Prader-Willi syndrome. *J Pediatr* 76:246-250
116. **Eiholzer U, Stutz K, Weinmann C, Torresani T, Molinari L, Prader A** 1998 Low insulin, IGF-I and IGFBP-3 levels in children with Prader-Labhart-Willi syndrome. *Eur J Pediatr* 157:890-893
117. **Lindgren AC, Hagenäs L, Müller J, Blichfeldt S, Rosenborg M, Brismar T, Ritzén EM** 1998 Growth hormone treatment of children with Prader-Willi syndrome affects linear growth and body composition favourably. *Acta Paediatr* 87:28-31
118. **Corrias A, Bellone J, Beccaria L, Bosio L, Trifirò G, Livieri C, Ragusa L, Salvatoni A, Andreo M, Ciampalini P, Tonini G, Crinò A** 2000 GH/IGF-I axis in Prader-Willi syndrome: evaluation of IGF-I levels and of the somatotroph responsiveness to various provocative stimuli. Genetic Obesity Study Group of Italian Society of Pediatric Endocrinology and Diabetology. *J Endocrinol Invest* 23:84-89
119. **Tauber M, Barbeau C, Jouret B, Pienkowski C, Malzac P, Moncla A, Rochiccioli P** 2000 Auxological and endocrine evolution of 28 children with Prader-Willi syndrome: effect of GH therapy in 14 children. *Horm Res* 53:279-287
120. **Partsch CJ, Lämmer C, Gillessen-Kaesbach G, Pankau R** 2000 Adult patients with Prader-Willi syndrome: clinical characteristics, life circumstances and growth hormone secretion. *Growth Horm IGF Res* 10:S81-85
121. **Høybye C, Frystyk J, Thorén M** 2003 The growth hormone-insulin-like growth factor axis in adult patients with Prader Willi syndrome. *Growth Horm IGF Res* 13:269-274
122. **Burman P, Ritzen EM, Lindgren AC** 2001 Endocrine dysfunction in Prader-Willi syndrome: a review with special reference to GH. *Endocr Rev* 22:787-799
123. **Grugni G, Marzullo P, Ragusa L, Sartorio A, Trifirò G, Liuzzi A, Crinò A; Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology** 2006 Impairment of GH responsiveness to combined GH-releasing hormone and arginine administration in adult patients with Prader-Willi syndrome. *Clin Endocrinol (Oxf)* 65:492-499
124. **Wollmann HA, Schultz U, Grauer ML, Ranke MB** 1998 Reference values for height and weight in Prader-Willi syndrome based on 315 patients. *Eur J Pediatr* 157:634-642
125. **Hauffa BP, Schlippe G, Roos M, Gillessen-Kaesbach G, Gasser T** 2000 Spontaneous growth in German children and adolescents with genetically confirmed Prader-Willi syndrome. *Acta Paediatr* 89:1302-1311
126. **Carrel AL, Myers SE, Whitman BY, Allen DB** 2002 Benefits of long-term GH therapy in Prader-Willi syndrome: a 4-year study. *J Clin Endocrinol Metab* 87:1581-1585
127. **Allen DB, Carrel AL** 2004 Growth hormone therapy for Prader-Willi syndrome: a critical appraisal. *J Pediatr Endocrinol Metab* 4:1297-1306

128. **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* 143:1456-1461.
129. **Whitman BY, Myers S, Carrel A, Allen D** 2002 The behavioral impact of growth hormone treatment for children and adolescents with Prader-Willi syndrome: a 2-year, controlled study. *Pediatrics* 109: E35
130. **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*. 146:570-577
131. **Tauber M, Barbeau C, Jouret B, Pienkowski C, Malzac P, Moncla P, Rochiccioli P** 2000 Auxological and endocrine evolution of 28 children with Prader-Willi syndrome: effect of GH therapy in 14 children. *Horm Res* 53:279-287
132. **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
133. **Butler MG, Theodoro M, Skouse JD** 2007 Thyroid function studies in Prader-Willi syndrome. *Am J Med Genet A* 143:488-492
134. **Festen DAM, Wevers M, Lindgren AC, Bohm B, Otten BJ, Maarten Wit J, Duivenvoorden HJ, Hokken-Koelega ACS** 2008 Mental and motor development before and during growth hormone treatment in infants and toddlers with Prader-Willi syndrome. *Clin Endocrinol* 68:919-925
135. **Festen DAM, de Weerd AM, van den Bossche RAS, Joosten K, Hoeve H, Hokken-Koelega ACS** 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
136. **Festen D, Hokken-Koelega A** 2007 Breathing disorders in Prader-Willi syndrome: the role of obesity, growth hormone treatment and upper respiratory tract infections. *Expert Rev Endocrinol Metab* 2:529-537
137. **Arens R, Gozal D, Burrell BC, Bailey SL, Bautista DB, Keens TG, Ward SL** 1996 Arousal and cardiorespiratory responses to hypoxia in Prader-Willi syndrome. *Am J Respir Crit Care Med* 153:283-287.
138. **O'Donoghue F, Camfferman D, Kennedy J, Martin A, Couper T, Lack L, Lushington K, McEvoy R** 2005 Sleep-disordered breathing in Prader-Willi syndrome and its associations with neurobehavioral abnormalities. *J Pediatr* 147:823-829
139. **Festen DAM, Wevers M, de Weerd ALW, van den Bossche RAS, Duivenvoorden HJ, Otten BJ, Maarten Wit J, Hokken-Koelega ACS** 2007 Psychomotor development in infants with Prader-Willi syndrome and associations with sleep-related breathing disorders. *Pediatr Res* 62:221-224
140. **Lindgren A, Hellstrom L, Ritzen E, Milerad J** 1999 Growth hormone treatment increases CO<sub>2</sub> response, ventilation and central inspiratory drive in children with Prader-Willi syndrome. *Eur J Pediatr* 158:936-940
141. **Myers S, Carrel A, Whitman B, Allen B** 2000 Sustained benefit after 2 years of growth hormone on body composition, fat utilization, physical strength and agility, and growth in Pder Willi syndrome. *J Pediatr* 137:42-49
142. **Haqq A, Stadler D, Jackson R, Rosenfeld R, Purnell J, LaFranchi S** 2003 Effects of growth hormone on pulmonary function, sleep quality, behavior, cognition, growth velocity body composition, and resting energy expenditure in Prader Willi syndrome. *J Clin Endocrinol Metab* 88:2206-2212

143. **Miller J, Silverstein J, Shuster J, Driscoll D, Wagner M** 2006 Short-term effects of growth hormone on sleep abnormalities in Prader-Willi syndrome. *J Clin Endocrinol Metab* 9:413-417
144. **Nagai T, Obata K, Ogata T, Murakami N, Katada Y, Yoshino A, Sakazume S, Tomita Y, Sakuta R, Niikawa N** 2006 Growth hormone therapy and scoliosis in patients with Prader-Willi syndrome. *Am J Med Genet A* 140:1623-1627
145. **De Lind van Wijngaarden RF, de Klerk LW, Festen DA, Hokken-Koelega AC** 2008 Scoliosis in Prader-Willi syndrome: Prevalence, effects of age, gender, body mass index, lean body mass and genotype. *Arch Dis Child* In press
146. **Odent T, Accadbled F, Koureas G, Diene G, Molinas C, Pinto G, Tauber M, Cournot M, Sales de Gauzy J, Glorion C** 2008 Scoliosis in patients with Prader-Willi Syndrome. *Pediatrics* In press
147. **Kroonen LT, Herman M, Pizzutillo PD, Macewen GD** 2006 Prader-Willi Syndrome: clinical concerns for the orthopaedic surgeon. *J Pediatr Orthop* 26:673-679
148. **Rees D, Jones MW, Owen R, Dorgan JC** 1989 Scoliosis surgery in the Prader-Willi syndrome. *J Bone Joint Surg Br* 71:685-688
149. **Accadbled F, Odent T, Moine A, Chau E, Glorion C, Diene G, Sales de Gauzy J** 2008 Complications of scoliosis surgery in Prader-Willi syndrome. *Spine* 33:394-401
150. **Farber C, Gross S, Neesen J, Buiting K, Horsthemke B** 2000 Identification of a testis-specific gene (C15orf2) in the Prader-Willi syndrome region on chromosome 15. *Genomics* 65:174-183
151. **Buiting K, Nazlican H, Galetzka D, Wawrzik M, Gross S, Horsthemke B** 2007 C15orf2 and a novel noncoding transcript from the Prader-Willi/Angelman syndrome region show monoallelic expression in fetal brain. *Genomics* 89:588-595
152. **Fillion M, Deal CL, Van Vliet G** 2006 Normal minipuberty of infancy in boys with Prader-Willi syndrome. *J Pediatr* 149:874-876
153. **Schmidt H, Schwarz HP** 2001 Premature adrenarche, increased growth velocity and accelerated bone age in male patients with Prader-Labhart-Willi syndrome. *Eur J Pediatr* 160:69-70
154. **Unanue N, Bazaes R, Iniquez G, Cortes F, Avila A, Mericq V** 2007 Adrenarche in Prader-Willi syndrome appears not related to insulin sensitivity and serum adiponectin. *Horm Res* 67:152-158
155. **Eiholzer U, Grieser J, Schlumpf M, l'Allemand D** 2007 Clinical effects of treatment for hypogonadism in male adolescents with Prader-Labhart-Willi syndrome. *Horm Res* 68:178-184
156. **Vestergaard P, Kristensen K, Bruun JM, Ostergaard JR, Heickendorff L, Mosekilde L, Richelsen B** 2004 Reduced bone mineral density and increased bone turnover in Prader-Willi syndrome compared with controls matched for sex and body mass index--a cross-sectional study. *J Pediatr* 144:614-619
157. **van Mil EG, Westerterp KR, Gerver WJ, Van Marken Lichtenbelt WD, Kester AD, Saris WH** 2001 Body composition in Prader-Willi syndrome compared with nonsyndromal obesity: Relationship to physical activity and growth hormone function. *J Pediatr* 139:708-714
158. **Butler MG, Haber L, Mernaugh R, Carlson MG, Price R, Feurer ID** 2001 Decreased bone mineral density in Prader-Willi syndrome: comparison with obese subjects. *Am J Med Genet* 103:216-222
159. **Hoybye C** 2004 Endocrine and metabolic aspects of adult Prader-Willi syndrome with special emphasis on the effect of growth hormone treatment. *Growth Horm IGF Res* 14:1-15

160. **Akefeldt A, Tornhage CJ, Gillberg C** 1999 A woman with Prader-Willi syndrome gives birth to a healthy baby girl. *Dev Med Child Neurol.* 41:789-790
161. **Prader-Willi Syndrome Association (New Zealand)** 2004 Inc Pickwick Papers.15:3
162. **Schulze A, Mogensen H, Hamborg-Petersen B, Graem N, Ostergaard JR, Brondum-Nielsen K** 2001 Fertility in Prader-Willi syndrome: a case report with Angelman syndrome in the offspring. *Acta Paediatr* 90:455-459
163. **Schrander-Stumpel CT, Sinnema M, van den Hout L, Maaskant MA, van Schrojenstein Lantman-de Valk HM, Wagemans A, Schrander JJ, Curfs LM** 2007 Healthcare transition in persons with intellectual disabilities: general issues, the Maastricht model, and Prader-Willi syndrome. *Am J Med Genet C Semin Med Genet* 145:241-247
164. **Hoybye C, Thoren M, Bohm B** 2005 Cognitive, emotional, physical and social effects of growth hormone treatment in adults with Prader-Willi syndrome. *J Intellect Disabil Res* 49:245-252
165. **Clarke DJ, Boer H, Chung MC, Sturmey P, Webb T** 1996 Maladaptive behaviour in Prader-Willi syndrome in adult life. *J Intellect Disabil Res* 40:159-165
166. **Dykens EM, Kasari C** 1997 Maladaptive behavior in children with Prader-Willi syndrome, Down syndrome, and nonspecific mental retardation. *Am J Ment Retard* 102:228-237
167. **Holland AJ, Whittington JE, Butler J, Webb T, Boer H, Clarke D** 2003 Behavioural phenotypes associated with specific genetic disorders: evidence from a population-based study of people with Prader-Willi syndrome. *Psychol Med* 33:141-153
168. **Clarke DJ, 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 Psychiatry* 180:358-362
169. **Dimitropoulos A, Blackford J, Walden T, Thompson T** 2006 Compulsive behavior in Prader-Willi syndrome: examining severity in early childhood. *Res Dev Disabil* 27:190-202
170. **Soni S, Whittington J, Holland AJ, Webb T, Maina E, 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* 51:32-42
171. **Soni S, Whittington J, Holland AJ, Webb T, Maina EN, Boer H, Clarke D** 2008 The phenomenology and diagnosis of psychiatric illness in people with Prader-Willi syndrome. *Psychol Med* 4:1-10
172. **Bailleul-Forestier I, Verhaeghe V, Fryns JP, Vinckier F, Declerck D, Vogels A** 2008. The oro-dental phenotype in Prader-Willi syndrome: a survey of 15 patients. *Int J Paediatr Dent* 18:40-47

**Table 1:** Indications for DNA testing.

<b>Age at assessment</b>	<b>Features sufficient to prompt DNA testing</b>
Birth to 2 years	- hypotonia with poor suck
2 - 6 years	<ul style="list-style-type: none"> <li>- hypotonia with a history of poor suck</li> <li>- global developmental delay</li> <li>- short stature and/or growth failure associated with accelerated weight gain*</li> </ul>
6 - 12 years	<ul style="list-style-type: none"> <li>- hypotonia with a history of poor suck (hypotonia often persists)</li> <li>- global developmental delay</li> <li>- excessive eating (hyperphagia, obsession with food) with central obesity if uncontrolled</li> </ul>
13 years through adulthood	<ul style="list-style-type: none"> <li>- cognitive impairment, usually mild mental retardation</li> <li>- excessive eating (hyperphagia, obsession with food) with central obesity if uncontrolled</li> <li>- hypothalamic hypogonadism and/or typical behaviour problems (including temper tantrums and obsessive-compulsive features)</li> </ul>

Adapted from Gunay-Aygun et al. (7) \* This feature has been added by the authors

**Table 2:** Management of GH treatment

<p>Before starting GH treatment:</p>	<ul style="list-style-type: none"> <li>- Genetic confirmation of Prader-Willi syndrome.</li> <li>- Evaluation of IGF-I status, and if possible GH status.</li> <li>- Nutritional evaluation and advice, and body composition if available (DEXA).</li> <li>- Prior control of food environment is vital especially in obese children.</li> <li>- Complete clinical evaluation including sleep and breathing studies if available. If sleep-disordered breathing, snoring or enlarged tonsils and adenoids are present, ENT assessment and polysomnography are mandatory.</li> <li>- OGTT particularly if obese and/or older than 2 years and family history of diabetes.</li> <li>- Family instruction on GH treatment including benefits and risks of the treatment and importance of careful monitoring.</li> <li>- Scoliosis evaluation including X-ray.</li> <li>- Evaluation of hypothyroidism (TSH, free T4, free T3) and commencement of replacement if appropriate.</li> </ul>
<p>On GH treatment:</p>	<ul style="list-style-type: none"> <li>- Regular clinical assessment of height, weight, BMI, body composition, pubertal status, scoliosis, IGF-I and side effects, every 3 to 6 months.</li> <li>- OGTT if previous impaired glucose tolerance, obese or family history of diabetes.</li> <li>- Ideally ENT assessment and polysomnography within the first 6 months.</li> <li>- If development or worsening of sleep-disordered breathing, snoring or enlargement of tonsils and adenoids, ENT assessment, polysomnography and IGF-I measurement are mandatory.</li> <li>- X-ray +/- orthopaedic assessment if concern or doubt about scoliosis.</li> <li>- Regular bone age determination particularly during pubertal age range.</li> <li>- Monitoring for hypothyroidism.</li> </ul>
<p>Cessation of GH treatment:</p>	<ul style="list-style-type: none"> <li>- Uncontrolled progression of obesity.</li> <li>- Continued worsening of glycemic control despite weight control, diabetic medication, and normal IGF-I.</li> <li>- Continued worsening of sleep disorder breathing despite weight control, tonsillectomy and adenoidectomy, and normal IGF-I.</li> <li>- Attainment of final height (but since there are potential benefits in adults on body composition, peak bone mass, cognition and quality of life, reassessment of persistent GH deficiency and replacement with adult doses may be warranted).</li> </ul>

**Table 3:** Ideal multidisciplinary team for children and adults with PWS.

The coordinator of the multidisciplinary team has traditionally been a specialist in genetics, paediatrics, endocrinology or learning disabilities. However the specific individual should reflect the person with the best experience, motivation, team working and managerial skills depending on local circumstances.

For children	For adults
Neonatologist	
Medical Geneticist *	Medical Geneticist *
Paediatric Endocrinologist *	Endocrinologist/Diabetologist*
Neuropaediatrician	Gynaecologist/Urologist *
Speech and language specialist	Cardiologist
ENT specialist	
Psychiatrist *	Psychiatrist *
Orthopaedist *	Orthopaedist *
Surgeon (for orchidopexy)	
Pneumologist	Pneumologist
Sleep disorder specialist	Sleep disorder specialist
Dentist	
Ophthalmologist	
Gastroenterologist	Gastroenterologist
Dietician*	Dietician *
Speech therapist	
Physical therapist	Physical therapist
Psychologist *	Psychologist *
Social worker *	Social worker *

\* indicates those particularly involved in transition

**Table 4:** Major recommendations for the management of PWS

- Early diagnosis in infancy using accredited genetic testing should be sought, and allows early intervention.
- Multi-disciplinary teams with experience in the management of PWS can provide best practice (Table 3).
- Family education and support, early intervention and individually-directed education is vital.
- Vigorous control of the food environment and regular exercise is essential to manage hyperphagia and obesity.
- GH therapy should be started early in childhood, taking into account cautions and relative contraindications (Table 2),
- Appropriate monitoring of GH replacement is essential (Table 2).
- Management of the transition from adolescence to adulthood requires specific attention and care, particularly with regards patient autonomy and endocrinological issues.
- Increased availability of group homes with experience in the management of PWS is needed to help placement, quality of life and health issues in adulthood.
- Recognition of the distinction between the underlying behavioural problems seen in PWS and acute psychiatric illness is essential.

**Table 5:** Areas of current uncertainty in the management of patients with PWS requiring further study.

- The best age at which to start GH therapy in childhood or infancy.
- The role for GH therapy in transition and adulthood.
- The indications and best regimen for sex steroid replacement.
- The pathophysiology of hyperphagia, and hence therapeutic possibilities.
- The pathophysiology of psychiatric and psychological illness, and hence therapeutic possibilities.