



## Meet the Expert Session

5:1 - 5:2

### Prader Willi syndrome: difficulties in clinical management

*Maithe Tauber, Toulouse, France*

Sunday September 21

11:00 - 12:00

Monday September 22

11:30 - 12:30

Topkapi B

## Management of children and adolescents with Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a complex neurodevelopmental genetic disorder that arises from lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13. The syndrome has characteristic phenotypes including severe neonatal hypotonia, early onset of severe obesity, short stature, hypogonadism, learning disabilities, behavioural problems and psychiatric phenotypes with severe consequences and difficult management issues for patients, families and carers. The lower limit of birth incidence is around 1 in 20,000 to 1 in 30,000 and population prevalence is about 1 in 50,000. Recent epidemiological studies surveys have highlighted the high rates of morbidity and mortality throughout life. PWS is a model showing that early diagnosis and comprehensive multidisciplinary approach including GH treatment prevent complications, optimise quality of life, and prolong life-expectancy. At this time we can assume that in these circumstances, we had completely modified the clinical presentation of most of the children with PWS. The same improvements are needed for adolescents and adult patients and require the experience of the paediatric endocrinologists.

**Early diagnosis:** 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 (1). The diagnosis of PWS should be evocated in all infants with severe and unexplained hypotonia (2). 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.

### **Management of children and adolescents presenting with PWS**

Early diagnosis offers the opportunity for education of parents (ie *parental guidance*), caregivers and other healthcare professionals to receive and give social, psychological and educational support. In addition, support from patient and family associations is increasingly available around the world. The strong efficacy of Growth Hormone (GH) treatment in these children explained the fact that paediatric endocrinologists are often in the first place to coordinate the care of these infants, children and adolescents. In adult patients the endocrinologists are also in the first row due to the complications of morbid obesity. At any age psychiatrists and psychologists are also needed. We like to say that the care of these patients is based on the core trio constituted by the paediatric endocrinologist, the endocrinologist and the psychiatrist.

**Infants:** Over the last ten years, the majority of cases are now diagnosed during the first months of life. 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. *Cryptorchidism* is present in over 80% of boys from birth and *orchidopexy* should be performed ideally during the first or the second year. Children with PWS have muscular hypotonia, decreased muscle mass, psychomotor delay, and reduced motor activity. Training programs, initiated early after birth 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. 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 to start very early in infancy combined with parental guidance to help with the impaired articulation and delay in development milestones seen in language acquisition.

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

**Natural history:** PWS has been classically described as having two phases: poor feeding and frequently failure to thrive (birth to early infancy) and onset of hyperphagia leading to obesity usually starting between 2 and 4 years. Recent examination of the natural history suggests a more complex progression leading to four main nutritional phases emphasizing the fact that weight increase precedes increase in calorie intake. *Neuroanatomical* abnormalities have been found in the post-mortem hypothalamus from patients with PWS that may underlie the hyperphagia, particularly low oxytocin cell number (4). In addition, fasting and post-prandial plasma levels of the orexigenic stomach-derived hormone ghrelin are greatly elevated in PWS throughout life (5), though do fall after food intake.

Although somatostatin acutely suppresses plasma ghrelin concentrations in PWS patients, appetite is not reduced in children or adults. *Body composition* studies show both increased body fat and reduced muscle in PWS from infancy to adulthood. There is also 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. *Type 2 diabetes mellitus* has been reported in around 25% of adults with PWS with a mean age of onset around 20 years but very few cases had been reported in children.

**Obesity management** : it 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, appropriate psychological and behavioural counselling of the patient and family. 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. Pharmacological treatment, including available anorexigenic agents, has not been of benefit in treating hyperphagia. Until now 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.

**Growth and GH status**: around 20% of neonates with PWS have a birth weight below -2SDS while median birth length is most frequently in the normal range. 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. Mean spontaneous adult height has been reported as around 160 cm in boys and 150 cm in girls. The serum levels of IGF-I are reduced in the majority of children and many adults even in obese patients. Spontaneous growth hormone secretion is reduced and GH peak during pharmacological stimulation test is less than 10 mcg/L in 80% of children. GH testing is not required before GH treatment but we advise to do one if possible.

**GH treatment in children**: the aims of GH treatment in children with PWS are to improve growth during childhood, adult height and body composition. In the USA, GH treatment is labelled for short stature while in Europe, growth retardation is not required in children with PWS for initiation of GH treatment. Using the currently recommended dose of 0.035mcg/kg/d, there is a significant increase in height, growth velocity and a decrease in percent body fat. Lean body mass increased significantly and this effect seems to be sustained. Only a few studies have reported data on adult height and most of them (44 patients) reached normal adult height, 60% in the KIGS study and 100% in a recent study. Prior improvements in strength and agility that occurred during the initial 2 years were sustained. These improvements during GH treatment might contribute to the higher quality of life and improved socialisation with reduced depression. 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 (6).

#### **Safety and GH treatment**

**Sudden death** : since October 2002, several reports of unexpected death in children with PWS have been published. A recent review including 64 children (28 on GH treatment) suggested a high risk period of death during the 9 first months of treatment (7). Nevertheless the role of GH in these deaths had not been proved. We advised that GH treatment should be started at a low dose, such as 0.009 to 0.012 mcg/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 effect 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). We think that these patients are highly fragile and that multidisciplinary care is mandatory to optimise the effect of GH.

**Sleep-related breathing disorders (SRBD)**: a variety of SRBD has been reported in PWS. Recently, it has been demonstrated that non-obese pre-pubertal PWS children have mainly central sleep apnoea and only rarely OSAS during the night. The number of central apnoea/hypopnoea (AHI apnea/hypopnea index) 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.

Five prospective studies have evaluated the effects of treatment with GH on breathing disorders in PWS. Most of the studies are in favour or either no effect of GH or a slight decrease in AHI. In light of these findings we suggest to perform a polysomnography prior GH treatment and to control it soon after the start of treatment (2 to 3 months). In case of difficult access, nocturnal oxymetry could be a minimum. Nevertheless in case of severe obesity or respiratory problems or snoring, the PSG is mandatory. Prior to PSG, ENT assessment with tonsillectomy or adenoidectomy if indicated should be performed. We advise to do this surgery in a children hospital with cardiac and respiratory monitoring. We think GH treatment should not be contra-indicated in children having an abnormal PSG without severe obesity, snoring, and with a normal ENT examination.

**Scoliosis :** Scoliosis is a frequent feature observed in about 40 % of children with PWS with or without GH treatment(8). Unlike idiopathic scoliosis, young children are also often affected, with no gender effect. We observed in our cohort a mean age at start of 7 yrs. Scoliosis is frequently associated with kyphosis particularly in obesity and appears to be bad a prognostic factor. The effect of BMI is not clear. Due to the high frequency of scoliosis even in infants, regular clinical assessment is required at each visit, whether or not they are receiving GH. In addition spinal X-ray and, if appropriate orthopaedic assessment, is advised prior to GH treatment at any age.. 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. Such surgery 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 implicates both central and peripheral origins at least in males. Most individuals will have no or delayed and incomplete puberty. Isolated premature pubarche and precocious puberty are not rare and there is no consensus as to management of either of these conditions. We used hydrocortisone in premature pubarche to decrease adrenal androgens when there is associated advancement of bone age. And we recommend to avoid the use of GnRH analogs in children with PWS and early or precocious puberty. 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. 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. 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.

**Hypothyroidism:** it has been reported in a low number of studies and is in our experience often under-evaluated or estimated in children with PWS. The prevalence varies from 6 to 30 % in children with PWS. A recent paper showed the occurrence of hypothyroidism on GH. 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.

**Transition into adult life:** continuing the benefits of early diagnosis and management 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. Health professionals, carers, patients and their families should be encouraged that the earlier diagnosis, multidisciplinary care and use of GH 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. 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.

This chapter did not develop the psychological and psychiatric aspects. A review with 175 references is in press : **Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M** 2008 Recommendations for the diagnosis and management of Prader-Willi syndrome *J Clin Endocrinol Metab* in press

#### References

1. **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
2. **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
3. **Goldstone AP** 2004 Prader-Willi syndrome: advances in genetics, pathophysiology and treatment. *Trends Endocrinol Metab* 15:12-20
4. Fegeirlova
5. **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
6. **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
7. **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
8. **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