# THERAPEUTIC APPROACH IN PRADER-WILLI SYNDROME

**Ionela Pascanu[1], Oana-Maria Căpraru[2], Otilia Marginean[3], Claudia Banescu[4]**

**Abstract**

Prader-Willi syndrome (PWS) is a genetic disorder characterized by absence of the active genes on chromosome 15. Symptoms appear since intrauterine development with decreased fetal movements, low birth weight and persist after birth with hypotonia, feeding difficulties and failure to thrive in the neonatal period. From infancy until adulthood, patients have short stature, become severely obese, with an insatiable appetite and food-seeking behavior. They also have psychiatric disorders, behavioral problems and learning disabilities. Treatment of these patients is multidisciplinary and several drugs have been studied in order to control appetite and reduce the morbidity of obesity, including cardiovascular and metabolic side-effects. The following paper offers an insight in the difficult management of the co-morbidities of Prader-Willi syndrome.

**Keywords** Prader-Willi syndrome, obesity, growth hormone, therapy

**Introduction**

Prader Willi syndrome (PWS) is the most common syndromic form of obesity. Its early description dates from 1887 when Langdon-Down described a girl with probable Prader Willi syndrome during adolescence, with mental impairment, short stature, hypogonadism and obesity. In 1956 Prader and his colleagues mentioned several other patients with similar phenotypes. In 1981, Ledbetter et al, described the microdeletions within chromosome 15 as site for PWS. PWS affects between 350 000 and 400 000 individuals worldwide and affects both sexes.

The diagnosis of PWS is suspected in patients who have characteristic clinical features and is confirmed by genetic testing. Affected pregnancies often exhibit reduced fetal activity with polyhydramnios and breech position. In 1993, Prader et al, developed clinical diagnostic criteria1, listed in Table 1. For children three years of age and younger, the diagnosis of PWS is highly likely if five points are scored among these criteria (four from major criteria). In children older than three years of age, eight points are required (five or more from the major criteria). Neonatal hypotonia is defined as the hallmark feature of this disorder and it is also a major cause of death because of asphyxia. Hypotonia determines also feeding difficulties with poor suck and failure to thrive. Soon after it was demonstrated that these criteria were too exclusive and they might have missed the diagnosis of PWS in patients with positive molecular testing. In 2001, Gunay-Aygun et al2 proposed a lower threshold for diagnostic DNA testing in patients with clinical features specific for their age, independent from the Prader criteria, as follows: neonates and infants up to two years old presenting hypotonia with poor suck; children between two and six years of age with hypotonia with history of poor suck and global developmental delay; children between six and twelve years old with history of hypotonia and poor suck, global developmental delay, hyperphagia with obesity if food is uncontrolled; children thirteen years old through adulthood with cognitive impairment, excessive eating, hypothalamic hypogonadism and/or typical behavior problems (temper tantrums, obsessive-compulsive features).

Prader Willi syndrome is the first genetic disorder attributed to genetic imprinting, meaning that the expression of genes depends on the gender of the parent donating the gene. PWS is caused by the absence of expression of the paternal active genes from the long arm of chromosome 15q11.2-13, either due to deletions of these regions from the paternal chromosome (approximately 78 percent of cases), maternal disomy (28 percent of cases) or rarely (fewer than 1 percent) defects in the imprinting center which determines a greater risk of recurrence in future siblings (up to 50 percent). Despite these defects, most of the cases of PWS arise sporadically. A standard diagnostic panel for PWS involves karyotype, fluorescence in-situ hybridization (FISH) followed by methylation studies and then micro-satellite probes to detect maternal uniparental disomy (UPD).

FISH analysis detects deletions, trans-locations or rearrangements on the chromosome 15q11.2-13. A negative FISH or karyotype analysis does not exclude the diagnosis of PWS and further investigations are needed.

Molecular analysis in PWS is highly sensitive and detects up to 99 percent of the cases and has become the "gold standard" technique to both confirm and reject the diagnosis of PWS. Methylation detects abnormal parent specific methylation imprinting within the PWS critical region on 15q11.2-13, the SNURF-SNRPN locus. This can be done by the Southern method using a methylation sensitive probe (SNRPN or PW71B) or by polymerase chain reaction (PCR) using parent specific primers.

[1]University of Medicine and Pharmacy, Târgu Mureş, Endocrinology Department,
[2] University of Medicine and Pharmacy Târgu Mureş, Department of Physiology,
[3] University of Medicine and Pharmacy Timisoara, Pediatrics Department,
[4]University of Medicine and Pharmacy, Târgu Mureş, Department of Genetics
Email: iopascanu@gmail.com, omcapraru@yahoo.com, omarginean@ymail.com, cbanescu@yahoo.com

If only a maternal pattern is present after methylation, PWS is confirmed. A positive DNA methylation analysis needs further investigations in order to distinguish between an imprinting defect or a maternal uniparental disomy. ***GH secretion in PWS patients***

Prader Willi syndrome is a complex and multi-systemic disorder and patients might exhibit endocrinopathies attributed to hypothalamic and pituitary dysfunction. Children with PWS have growth failure, altered body composition with increased in the fat mass, decreased lean body mass, reduced bone density with increased risk for osteoporosis, hypogonadism which might worsen the bone density, sleep disorders, behavioral and psychiatric problems and learning disabilities.

Intrauterine growth restriction is common, with a birth weight of -1.37 standard deviation (SD) score and median birth length of -0.46 SD score(3). After birth short stature is also a common feature, especially in the first two years of life and the average final height in adult PWS patients has been reported as 162 cm in boys and 150 cm in girls(4) . Growth hormone secretion is generally blunted in PWS patients and GH peak during pharmacological stimulation tests fails to rise above 10 μg/l. The exact mechanism responsible for the GH deficiency is unknown, and several hypothesis have been proposed. One of them is related to the ghrelin level. Ghrelin produced by the stomach when fasting, is an endogenous ligand for the receptor responsible for the growth hormone secretion, GH secretagogue receptor (GHS-R) from the hypothalamus and pituitary gland. An independent effect of ghrelin observed in rodents is that it induces adypogenesis and infusion of ghrelin enhances appetite and increases food intake. In obese patients, ghrelin levels are low while in patients with weight loss and anorexia nervosa, levels tend to be higher. Despite these observations, patients with PWS have extremely high levels of ghrelin via an unknown mechanism, which might be implicated in the pathogenesis of the hyperphagia, GH deficiency or the reduced levels of GHS-R (5). Hyperghrelinemia is not a consequence of GH deficiency since GH replacement therapy does not reduce the levels of ghrelin. Ghrelin is transported into the brain where stimulates neurones from the arcuate nucleus and thus makes part of a circuit involving the energy homeostasis, stomach and hypothalamus (6). However, other causes of growth failure should be excluded including hypothyroidism and under-nutrition (a young child who fails to thrive or in case of a restricted calorie diet).

Children with genetically confirmed PWS are candidates for treatment with GH which was approved by the United States Food and Drug Administration (FDA) in 2000 and has been approved for this use in most countries. It is generally not necessary to evaluate formally for growth hormone deficiency before considering treatment (3). Growth failure is typically defined as decreased linear growth velocity or decreased height in comparison with the mid-parental height (MPH) prediction. Measurement of insulin-like growth factor-1 (IGF-1) and insulin-like binding protein-3 (IGFBP-3) are sometimes used to appreciate the correct growth hormone dose.

Treatment with GH has beneficial effects on linear growth, body composition, osteoporosis and bone mineral density along with language acquisition, gross motor skills and cognitive scores (7). The optimal age to begin treatment, dosing and duration of therapy have not been established but there is increasing evidence that early initiation of GH treatment, before two years of age, improves clinical outcomes (8). Initiation before the age of 18 months old was associated with accelerated acquisition of mobility skills compared to controls of the same age, improvement in behavior with lack of behavioral deterioration during adolescence (9). The response to growth hormone treatment is greatest in the first 12 months and persists for as long as five years. Even with long term GH treatment, body composition is not completely normalized and adult PWS subjects, especially men, failed to improve bone mass with GH treatment for two years in a recent study (10). Regarding the final height after treatment with GH, the results are astonishing in the Kabi International Growth Study (KIGS) database (11) and show that children treated with GH for 6.9 years reached the adult height within MPH.

Because of several reports(12) of unexpected deaths coinciding with the use of exogenous GH, FDA has added labeling to GH products stating that they are contraindicated in high risk PWS patients with severe obesity (weight > 225 percent of ideal body weight), diabetes, respiratory compromise or severe sleep apnea. The deaths were mostly associated with respiratory problems and most occurred within the first nine months of treatment, with a median of three months and supported the hypothesis that GH might have a possible role in worsening respiratory complications at the start of treatment (12). Growth hormone has mixed effects on breathing problems especially during sleep; it may worsen obstructive apnea by stimulating adenotonsillar hypertrophy. Otherwise, GH has direct effects on hypothalamic function improving the central hypoventilation. Unexpected deaths were also reported in children with PWS without GH treatment suggesting that PWS patients have an increased risk of death independent of treatment with GH products, most of the deaths being related to a complicated respiratory tract infection, hypoventilation, obstructive sleep apnea, chocking episodes, acute gastric distension/rupture and necrosis, septicemia or cardiac events. In the same review, Tauber et al(12) found that the ratio between males and females was 2:1 suggesting that boys with PWS are at greater risk of death.

Before starting GH treatment, patients should be evaluated for upper airway obstruction or apnea (with the use of polysomnography), glucose intolerance and scoliosis because of the possibility of aggravation of these conditions.

For all these reasons, it is advised to start treatment with a low dose, 0.25-0.3 mg/m2/day or 0.009-0.012 mg/kg/day, increasing during the first weeks and months to reach the standard replacement dose. The currently recommended dose is 1.0 mg/m2/day or 0.035 mg/kg/day (3) and the dose should be adjusted with changes in body weight during the course of therapy. The dose might be adjusted to achieve IGF-1 levels in the normal range to optimize linear growth and minimize risks of adverse

metabolic side effects. It is recommended to avoid high IGF-1 levels, especially if there are clinical suspicions of overtreatment (edema, worsening of snoring, headache, acromegalic clinical features) (3). Children with abnormal polysomnograms should be followed up monthly and the treatment should be ceased if they develop intercurrent respiratory tract infections and increased obstructive symptoms. Careful monitoring is recommended for infants who are at greater risk of respiratory compromise because of the general hypotonia. They should have a constant monitorization of the oxygen saturation during sleep for the first one to two months after starting treatment.

Cessation of GH treatment is also recommended if the patient presents uncontrolled progression of obesity despite controlled food intake, worsening of glycemic control despite diabetic medication and attainment of adult final height.

It has not been established whether continuation of GH treatment in adulthood has beneficial effects, but the modest benefits in body composition, cognition, quality of life and peak bone mass raise the possibility of continuation of GH treatment even after epiphyseal closure.

**Obesity and hyperphagia treatment**

In an extensive cohort study, Jennifer Miller et al(13), demonstrated that PWS is characterized by several gradual nutritional phases. Phase 0 occurs in utero with reduced fetal movement and growth restriction, with a mean body weight of 2.8 kg at term, often associated with polyhidramnios. Phase 1 consists of severe neonatal hypotonia, hyporeflexia, without onset of obesity. Subphase one requires frequent assisted feeding for up to 3-4 months of age because of poor suck with or without failure to thrive. Subphase two is characterised by a normal development, a normal growth and a steady weight curve. Starting nutritional phase two, which usually starts at a mean age of 2 years, weight slowly increases. In subphase one the total body weight increases without increasing calorie intake and appearance of food cravings. It has been shown that at this point, with early counseling, calorie restriction and dietary recommendations, it is possible to maintain a normal weight reported to height. In subphase two, the child starts to develop abnormal interest in food which serves to a worsening of their existing obesity, but without unrelenting appetite. Phase three is the most aggressive nutritional status in PWS patients and has been described from 3 up to 15 years of age, with a median age of onset of 8 years old. It is the classical phase with hyperphagia, increased calorie intake, aggressive food seeking, reduced energy expenditure and satiety. A restrictive food environment is highly recommended, with food storage being locked, access to food or money to buy food being forbidden and constant supervision employed whenever possible(3). Some adults progress to a phase 4 when the insatiable appetite disappears and the patient regains his satiety sensation.

A major concern in PWS patients has been the motor performance. Even though at birth newborns are severely hypotonic, after several months of life the muscle tone improves but still they suffer from muscle weakness and delayed motor development. Persistence of these problems has been reported in childhood and adulthood, with decreased physical activity and low scores on standardized performance tests (14). The cause of these abnormalities is unknown but it could be related to the abnormal body composition and neuromuscular functioning. It has been thought that muscle hypotonia might be due to a central nervous system abnormality, but Sone(15) suggested that there is a primary muscle pathology with muscle fiber immaturity and abnormal muscle fiber type distribution.

Studies of body composition with the aid of body dual-energy X-ray absorptiometry (DEXA) have demonstrated that despite their adiposity, patients with PWS have decreased visceral fat, which protects them from the negative effects of the metabolic syndrome: type 2 diabetes, insulin-resistance and dislipidemia. Adipose tissue is thought to be an endocrine organ capable of producing a variety of cytokines and hormones, of interest being adiponectin. Adiponectin has antidiabetic and antiatherogenic properties and thus, obese patients with type 2 diabetes or cardiovascular diseases usually have hypoadiponectinemia. Kennedy et al (16) has shown that levels of adiponectin are lower in PWS patients compared to lean subjects but are higher than control obese patients. A variety of gastrointestinal peptides have been studied among patients with PWS: pancreatic polypeptide, cholecystokinin and ghrelin. The mechanism that causes impaired satiety and hyperphagia is not completely understood though the role of ghrelin as a primary or secondary factor in satiety defect is unclear. Some authors proposed that a surge in ghrelin might precede the hyperphagia and obesity observed in older children(16). As pharmacoherapy, somatostatin analogs suppress plasma ghrelin concentrations in PWS patients but fail to reduce the appetite and further studies showed no benefit of chronic administration of these agents (17).

Traditionally, the mainstay of management has centered on early institution of a low-calorie diet with regular exercise, rigorous supervision, restriction of food and money, and appropriate psychological and behavioral counseling for the patient and family, often in the context of group homes for PWS adolescents and adults(3).

Pharmacological treatment in PWS patients, especially children is not an accepted choice of treatment since there there is little evidence that these drugs have specific effects on binge eating or weight gain. Different drugs have been tried, like selective serotonin reuptake inhibitors (SSRIs) or topiramate, a novel anticonvulsivant, which did not decrease appetite, food intake or weight status although it decreased self-injurious behaviors, such as skin-picking.

Since dietary restriction or appetite suppressing agents are ineffective, surgical weight loss procedures have been also tried but there are scattered case reports, most with follow-up of less than 2 years and results seem to be inconsistent.

Patients that qualify for bariatric surgery are those with a BMI over 40 kg/m2 with medical conditions or those with a BMI of over 50 kg/m2, children who have reached their physical maturity (Tanner stage 4 or 5), emotional and cognitive maturity and those who have been unable to loose

weight by all other measures. Guidelines recommend against bariatric surgery for prepubertal children, untreated psychiatric conditions, Prader-Willi syndrome or eating disorders(18). Bariatric procedures for weight loss are divided in malabsorbtive, restrictive or a combination of both. Surgical procedures that restrict the stomach may be particularly risky for patients with PWS as there are reports of gastric dilatation and necrosis. A variety of bariatric techniques have been implemented but the ideal procedure is still controversial(19). Since ghrelin is involved in hyperphagia and the lack of satiety, surgical procedures reducing its levels proved to be efficacious in reducing body weight at the expenditure of malabsorbtion, diarrhea, vitamin B12, iron and folate deficiency, bone demineralization and osteoporosis, hypoalbunemia and protein malnutrition(20). Even though, reports have shown a little reduction in body weight but an improved quality of life. A recent clinical report(21) on three patients with PWS treated with laparoscopic mini-gastric bypass (LMGBP) and laparoscopic sleeve gastrectomy (LSG) demonstrated significant reduction of body weight and serum ghrelin after a follow up of 33 months. The main advantage of these procedures is that ghrelin serum level is reduced by removal of gastric fundus and reduction of ghrelin apparently corrects hormonal abnormalities in PWS patients.

***Steroid treatment and puberty induction***

Hypogonadism in PWS patients has four phenotypes characterized by the analysis of FSH and Inhibin B, which suggest both a hypothalamic and a peripheral cause(22): primary hypogonadism, central hypogonadism, partial gonadal and central dysfunction, mild central and severe gonadal dysfunction; testosterone levels are usually low and estrogen levels are in the normal range of the follicular phase. Hypogonadism manifests early in infancy by genital hypoplasia in females, micropenis and/or cryptorchidism in boys, for which they generally need correctional surgery in the first year of life; the Committee on Genetics, American Academy of Pediatrics recommends an initial course of medical treatment with human chorionic gonadotropin (hCG) before surgery, in order to avoid general anesthesia which might aggravate respiratory infections due to hypotonia(23). Besides descent of the testes, hCG treatment also contributes to the normal development of the scrotum and has a good prognosis on the final penile length.

| **Major criteria (1 point each)** |
|---|
| Neonatal and infantile central hypotonia, gradually improving with age |
| Feeding problems in infancy with need for special feeding techniques and poor weight gain/failure to thrive |
| Excessive weight gain between 12 months and 6 years of age; central obesity in the absence of intervention |
| Characteristic facial features (three or more of the below)<br>Dolichocephaly (infancy)<br>Narrow face or bifrontal diameter<br>Almond-shaped eyes<br>Small-appearing mouth with thin upper lip - *(Figure 1)*<br>Down-turned corners of mouth |
| Hypogonadism, with any of the following<br>Genital hypoplasia (hypoplasia of labia minora)<br>Delayed or incomplete maturation with delayed pubertal signs in the absence of intervention after 16 years of age (amenorrhea after age 16) |
| Mild to moderate mental retardation or learning problems in older children (QI= 69) |
| Hyperphagia/food foraging/obsession with food |
| Deletion 15q11-13 (or other cytogenetic/molecular abnormality of the Prader-Willi chromosome region) |
| **Minor criteria (1/2 point each)** |
| Decreased fetal movement or infantile lethargy or weak cry in infancy, improving with age |
| Characteristic behavior problems–temper tantrums, violent outbursts, and obsessive-compulsive behavior; tendency to be argumentative, oppositional, rigid, manipulative possessive, and stubborn; perseverating, stealing, and lying (5 or more of these symptoms required) |
| Sleep disturbance and sleep apnea |
| Short stature for genetic background by age 15 (in the absence of growth hormone intervention) |
| Hypopigmentation—fair skin and hair compared with family |
| Small hands (<25th percentile) and/or feet (<10th percentile) for height age – *Figure 1* |
| Narrow hands with straight ulnar borders |
| Eye abnormalities (esotropia, myopia) |
| Thick viscous saliva with crusting at corners of the mouth – *Figure 2* |
| Speech articulation defects |
| Skin-picking |

***Table 1.*** Diagnostic criteria for Prader-Willi syndrome. Major criteria are weighted at one point each and minor criteria are weighed at one half point. Major criteria must comprise ≥ five points of the total score (Holm *et al* [1], 1993).

Premature pubarche has been described, due to an early maturation of zona reticularis, but it is not sustained and it does not need treatment with GnRH analogs. Obese PWS girls may have pseudo-pubertal development with vaginal bleeding mimicking monthly menses but without ovulation. This is due to aromatization in the adipose tissue of adrenal steroids to estrogens which determine endometrial estrogenisation and breakthrough bleeding. LH levels in PWS patients are low and this explains the injury of the germ cells and defects in the spermatogenesis. Correction of the gonadal axis may be achieved with a course of treatment with clomiphene citrate which raises testosterone and both serum and urinary gonadotropin levels.

Treatment of hypogonadism in PWS is still controversial and there is no consensus for the management of this condition. At some point they will need sexual steroid replacement therapy regardless of their mental retardation, especially if there are signs and symptoms of hypogonadism: lack of sexual secondary development, amenorhea/oligomenorrhea or decreased bone density. Replacement doses should be titrated to the individual's response since there are concerns about effects on mood and behavior. Care should be given to females with menses since hygiene issues might be difficult to manage. Transdermal estrogen preparations are well tolerated despite the skin picking. For testosterone replacement therapy both transdermal and intramuscular preparations are a good choice of treatment. The dose should be lower than the normally recommended (one third to one half) and titration is important to prevent the aggressive behavior occasionally seen in some individuals. PWS girls with regular menses and sexual maturation should benefit from sexual counseling and appropriate contraceptive treatment because even though they are sterile, pregnancies have been reported(24); specialists usually advise against conception due to the high risk of recurrence of the disease in the offspring (3). Paternity in PWS patients has not yet been reported. Because of their hypogonadism and increased risk for osteoporosis, yearly evaluation of BMD by dual-energy X-ray absorptiometry (DEXA) is recommended(3).

As mentioned, PWS patients have hypothalamic dysfunctions therefore the clinical manifestations of pituitary hormone deficiency are expected. Under normal conditions, the secretion of cortisol is controlled by the adrenocorticotropic hormone (ACTH). Clinical manifestations of adrenal insufficiency are uncommon in PWS patients but various dynamic tests demonstrated that patients with PWS cannot provide a stress induced rise in cortisol similar to a normal person. A study from 2008, reported a 60% prevalence of central adrenal insufficiency (CAI) in children with PWS(25). Based on similar reports, it has been suggested the treatment with hydrocortisone during acute illness unless CAI has been ruled out.

***Orthopedic treatment***

Frequently observed in PWS patients are severe deformities of the spine in both frontal and sagittal plan. Scoliosis is one of them, its incidence is 30-70%(26) and it increases with age. Because of their obesity, a clinical diagnosis of scoliosis in PWS patients is sometimes difficult so radiographic evaluation is needed. A risk of aggravating the scoliosis was thought to be the height velocity in patients treated with growth hormone, but recent studies have not confirmed this suspicion(27). Scoliosis is frequently associated with kyphosis which explains the risk for development of severe progressive cervical thoracic kyphosis in those treated surgically.

Bracing, as a treatment, is controversial because moulding is difficult especially in those with severe obesity and lack of compliance. Remodeling is therefore often necessary in about 15-20% of patients, especially in those with unbalanced and progressive curves, respiratory dysfunctions and cardiocirculatory restrictions. Retrospective studies have shown that growing spinal implants are safer and produce less complications (delayed wound healing, temporary paraplegia, deep infections, pseudoarthrosis), in the treatment of early-onset scoliosis (28). Nevertheless, there is no consensus on the management of scoliosis and the ideal remodeling surgical procedure.

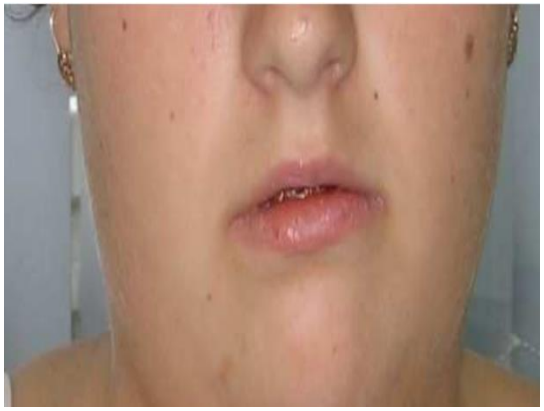

***Figure 1***. *Small-appearing mouth with thin upper lip and thick viscous saliva with crusting at corners of the mouth in a 16 years old girl with PWS*

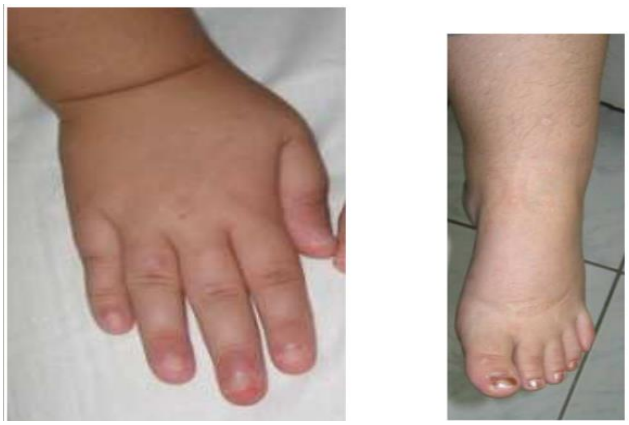

***Figure 2***. *Small hands (<25th percentile) and/or feet (<10th percentile) for height age from the same 16 years of age girl with PWS*

***Sleep apnea and respiratory dysfunctions***

Patients with PWS are at increased risk of sleep disturbances including central apnea, obstructive apnea and narcolepsy. Obstructive sleep apnea is caused by adenotonsillar hypertrophy, kyphoscoliosis, thick and sticky saliva, hypotonia of the respiratory muscles and also by the narrow upper respiratory airways. Sleep disordered breathing occurs in at least 70% of children and young adults with PWS, and is associated with increased daytime sleepiness, behavioral problems, increased risk for cardiovascular complications, cor pulmonale or pulmonary hypertension, aggravation of arterial hypertension or diabetes mellitus. It is recommended to monitor all patients with PWS for sleep related disturbances, snoring, apnea for more than five seconds or daytime sleepiness, particularly during intercurrent respiratory infections. Patients with severe obesity and clinical symptoms of sleep apnea should be further evaluated for adenotonsillar hypertrophy and also referred to a polysomnogram. In patients with severe obstructive sleep apnea, tonsillectomy, adenoidectomy or tracheostomy placement may be necessary.

***Psychiatric treatment***

PWS patients are well known for their reduced Intelligence Quotient (IQ) but despite this, they have a good developed long term memory, visual spacial performances and they also may have a high interest in puzzles. Scientists have identified a characteristic pattern of behavior and psychiatric problems. The cardinal aspect in PWS is the hyperphagia and all the preoccupations regarding food: stealing money to buy food, hiding food, scavenging, eating raw, spoiled or frozen food and sometimes having picas. Besides this, PWS patients exhibit other behavioral problems, temper-tantrums, emotional lability, impulsiveness, aggressiveness, bipolar disorders, compulsive behavior and physical injury such as skin-picking which is present in up to 96 % of patients and is generally related to boredom and anxiety (3). Since the etiology is elusive, the management of these disorders is usually environmental and behavioral. There are few studies regarding safety of psychiatric medication for PWS patients except from antidepressants and antipsychotics which are a better choice than mood-stabilizing medication (29). As described above, medical treatment has little or no effect on hyperphagia and insatiable appetite but reduces the self-injurious behavior (skin-picking).

**Conclusions**

Since there is no cure for Prader Willi syndrome, the major interest in the management of this disorder is the development of sensitive genetic testing modalities to allow early diagnosis and intervention to improve the quality of life of both the patients and their families and reduce though, the high risk of morbidities and mortality. PWS patients need a multidisciplinary team and pharmacological, surgical and environmental treatment. Despite the reported side effects, growth hormone still plays an important role in the management of these patients, and early use helps them to achieve their final adult height, improves the body composition with reduction of the adipose tissue and increase of the lean mass. Anorexigenic agents failed to treat hyperphagia and treatment of obesity sometimes needs restrictive bariatric surgery along with a better food control, restrictive calorie diet, physical activity and rigorous supervision. There are still unknown mechanisms implicated in the pathophysiology of this syndrome, so further studies are needed to establish the exact cause of the signs and symptoms of PWS in order to develop target pharmacological treatment.

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**Correspondance to:**

Ionela Pascanu MD, PhD,
University of Medicine and Pharmacy
Endocrinology Department,
38 Gh. Marinescu Str.,
Targu Mures 540139, Romania
Email: iopascanu@gmail.com