Endocrine management of children with Prader–Willi syndrome

Abstract: Prader–Willi syndrome is a rare genetic condition affecting nearly 1/15,000 live births. Clinical features include neonatal hypotonia, poor weight gain in early infancy followed by binge eating from childhood to adulthood, severe obesity, developmental delay, short stature, and hypogonadism of both central and peripheral etiology. Central hypothyroidism and adrenal insufficiency may occur. Sleep disordered breathing, by obstruction of upper airways associated with central hypventilation, is a common feature. Most of these characteristics are assumed to be the result of a hypothalamic dysfunction. The most important complication and the most difficult to manage is the obesity. This review aims at discussing the most recent strategies to manage the endocrine complications of Prader–Willi syndrome patients, with a special approach on the treatment of obesity, hypogonadism, and short stature. We summarize the indication and effects of recombinant human growth hormone therapy on growth, cognitive development, and body composition, and discuss the effects of recombinant human growth hormone therapy on the resulting sleep disorders.

Keywords: Prader–Willi syndrome, obesity, hypogonadism, growth hormone, sleep disorder

Introduction

Prader–Willi syndrome (PWS) is a rare genetic disorder caused by a lack of expression of paternally inherited imprinted genes located on chromosome 15q11-q13, and it is characterized by hypothalamic dysfunction. The clinical findings include dysmorphic facial features (thin upper lip and almond-shaped eyes), neonatal hypotonia, poor sucking and weight gain in early infancy followed by binge eating and severe obesity, developmental delay, short stature, small hands and feet, and hypogonadism. Other endocrine deficiencies may occur, such as hypothyroidism and partial adrenal insufficiency. Most of these features are assumed to be the result of hypothalamic dysfunction. Due to the association of hypotonia and obesity, sleep apnea is a major concern. PWS has a similar prevalence between genders and occurs worldwide with an incidence of 1/15,000 to 1/25,000. It should be suspected in all children with severe hypotonia at birth, as well as among children who have difficulty gaining weight in the first year of life, and signs of hypogonadism like cryptorchidism and micropenis. These children should be referred for molecular testing for definitive diagnosis.

The most common genetic finding (70% of cases) in this population is the deletion of paternally inherited genes, followed by (25% of cases) paternal uniparental disomy (when the child receives both copies of chromosome 15 from the mother and none from the father). Five percent of cases are due to errors of imprinting, and in rare cases is...
associated with a translocation, which moves the gene away from the center of the imprinting region. The most common method to diagnose PWS is fluorescence in situ hybridization, although the most accurate method is deoxyribonucleic methylation analysis.

In the long term, the greatest challenge faced by the caregivers and the health professionals involved with these patients is how to control the severe obesity and its metabolic complications. The awareness about this problem should start as early as the PWS diagnosis is made, even during the period when the affected individual experiences difficulty gaining weight, and this symptom is of capital importance since it represents the major cause of morbidity and mortality of these patients.

The objective of this review is to discuss the most recent strategies to manage the endocrine complications found in PWS.

**Obesity**

The natural history of PWS is marked by distinct nutritional stages. Classically divided into two stages (poor feeding and overfeeding), the nutritional phases of children with PWS are more complex. In 2011 Miller et al identified up to seven phases. The first of these phases is intrauterine, where fetuses with PWS have decreased fetal movements and growth restriction compared to unaffected siblings (PWS children are 15%–20% smaller than their unaffected siblings). During the next two phases, which are detected in the first years of life, the child is not obese. These phases that are characterized by normal weight are followed by the four phases where the PWS patient is already obese, although he or she is exhibiting different behaviors towards caloric intake. During the first year of life, hypotonia with severe difficulty to feed with or without failure to thrive is characteristic. During infancy, most patients with PWS weigh between the 25th and the 75th percentile of the growth chart for healthy children. Later, there is a gradual increase in weight gain, initially without noticeably significant changes in appetite or caloric gain. After 5 years of age, the PWS patient goes into a phase of hyperphagia, which is typically accompanied by a lack of fullness and binge eating. During this period, the child presents with behavioral changes related to diet, which include actively seeking food, eating inedible food (animal feed, spoiled food, decor that mimics food, garbage, and so on), stealing food or money to purchase food, and even escaping from home to actively pursue aliments. The cause for the delay in the development of the hyperphagia and changes in feeding behavior remains uncertain, and it is most possibly related to delayed or abnormal central nervous system development, rather than hormonal peripheral nervous system alterations. Ghrelin, although increased in patients with PWS, does not seem to play an important role in the etiology of obesity in these patients.

The amount of calories ingested is not the only characteristic that leads to obesity in PWS patients. When compared with other individuals with similar weight and body mass index (BMI), PWS patients have lower resting energy expenditure. They also have differences in the lean-to-fat mass ratio and in fat distribution. Even though the lean-to-fat mass ratio favors the fat mass, with reduced lean body mass and increased fat mass, PWS patients seem to be partially protected from the metabolic complications associated with the degree of obesity. A study by Goldstone et al evaluated the distribution of adipose tissue in obese women with and without PWS through magnetic resonance imaging and revealed a peculiar pattern of visceral fat distribution in carriers of the syndrome, with decreased visceral adipose tissue and increased subcutaneous adipose tissue. It has been proposed that these patients have lower serum insulin and insulin resistance when compared to their peers. Thus, the relative decrease of visceral fat appears to protect patients with PWS from some obesity-related complications. However, type 2 diabetes (25%), hypertension and cardiovascular disease (38%) are described in adults with PWS.

Grugni et al compared the frequency of metabolic syndrome components in 108 adult patients with PWS (87 obese patients and 21 nonobese patients) with 85 obese nonsyndromic patients. The study revealed that obese patients with PWS have a higher frequency of hyperglycemia and elevated systolic blood pressure when compared with obese controls. However, the presence of metabolic syndrome was higher in controls (45.9%) than in both nonobese patients with PWS (4.8%) and obese PWS patients (41.4%).

The management of obesity in PWS involves early diagnosis, the use of a low calorie balanced diet, monitoring with a multidisciplinary team, family psychological counseling, and behavioral guidance regarding the disease and the inevitable hyperphagia. The tools used to control weight gain include strict supervision with controlled access to food and regular exercise. Recombinant human growth hormone (rhGH) therapy may help since it may reduce fat mass, increase muscle mass, increase muscular tone, and consequently increase energy expenditure, although it does not change hyperphagia.

Maintaining adequate nutrition and appropriate monitoring of weight gain in children with PWS at any age is...
essential. This goal is achieved through behavioral and dietary management; thus, the diet should be adjusted to maintain an adequate weight for the patient’s age. When the hyperphagic behavior begins, calories should be restricted to 60% of the calories recommended for each patient’s age group. The recommended diet consists of 30% fat, 45% carbohydrates, and 25% protein, with at least 20 grams of fiber per day. In the study by Miller et al, 33 PWS patients who had undergone this diet had more success in terms of weight management than those having only a restricted amount of total calories.

Regarding behavioral change, it is extremely important to restrict access to food and, if necessary, the locking of cabinets and refrigerators is indicated. Moreover, caregivers should avoid exposure of children to places that suggest eating, encourage a routine in terms of when and what to eat, and caregivers should also be instructed to avoid offering food to the child.

The practice of sports and physical activity is essential for the patient with PWS, since it stimulates energy expenditure, promotes socialization, and increases muscle tone. The choice of sports should be individualized according to the local availability and preference of the child; moreover, the routine of the patient with PWS should include at least 30 minutes of participation in some form of physical activity, including sports, 4-5 days per week.

Published controlled trials showed no evidence of benefits in terms of the pharmacological treatment of hyperphagia with anorectic agents such as sibutramine or topiramate. Studies describing the use of agents that could reduce serum ghrelin levels, like somatostatin, also failed to demonstrate any benefit in PWS. A recent study with glucagon-like peptide-1 analog in eight patients with PWS showed a sharp increase in satiety and insulinohippotropic effects, as well as a decrement in serum glucose. However, further studies are necessary to assess the safety and efficacy of this class of drugs, since it causes delayed gastric emptying and results in an increased risk of gastric necrosis and/or rupture secondary to binge eating.

Bariatric surgery and gastric banding or bypass, as alternatives for the treatment of severe obesity in patients with PWS, have disappointing results, since these procedures do not reduce hyperphagia and do not cause weight loss over a long period of time. It is noteworthy that these procedures are still associated with high mortality, since the patient with PWS has greater resistance to pain, reduced satiety, autonomic dysfunction, delayed gastric emptying, decreased ability to vomit, self-flagellation, sleep disorders, and increased risk during anesthetic induction. Thus, there is little justification for using bariatric surgery as routine treatment in severely obese patients with PWS.

**Hypogonadism**

The majority of patients with PWS have clinical signs of hypogonadism from birth, such as cryptorchidism, which is present in 80%-90% of cases; micropenis; and hypoplasia of the scrotum, of the clitoris, and of the labia minora. In adolescence, delayed pubertal development or incomplete puberty is common, although there are reports in the literature of premature adrenarche and precocious puberty. The common knowledge is that PWS patients have hypogonadotropin hypogonadism due to hypothalamic dysfunction, with normal prepubertal testicular histology documented. Currently, however, there is evidence that primary testicular dysfunction, mainly due to tubular injury, greatly contributes to the hypogonadism observed in boys. In a study published in 2012, Siemensma et al followed 68 patients with PWS for 8 years (with a mean age of 3.4 years at the initial visit), and noted that after the onset of puberty, inhibin B levels declined to below the 5th percentile, and follicle-stimulating hormone (FSH) levels increased to above the 95th percentile. Testosterone levels increased, but remained below the 5th percentile, suggesting primary testicular failure. In women, there is greater phenotypic variability in relation to ovarian function. Recently Radicioni et al and Gross-Tsur et al confirmed the heterogeneity of the reproductive hormone profile in patients with PWS.

After the clinical or genetic diagnosis, proper management of cryptorchidism is extremely important since there is evidence of early damage of germ cells. The Committee on Genetics of the American Academy of Pediatrics recommends the use of chorionic gonadotropin prior to definitive surgical treatment to avoid possible deleterious effects of general anesthesia in children with muscular hypotonia. In addition, chorionic gonadotropin can increase the size of the scrotum and partially normalize the length of phallus, improving surgical outcomes. Preferably, this should be initiated between 6 months and 12 months of age. During clinical treatment, it is important to follow serum testosterone levels and testicular ultrasound. If medical treatment is not successful, it is recommended that orchiopexy be conducted before the patient reaches 2 years of age.

During puberty, hormone replacement therapy should be considered for the induction, promotion, and maintenance of puberty with the goal of preventing decreased bone mineral density (BMD). There is no consensus as to the most appropriate regimen for sex hormone replacement; however, before...
any treatment is used, it is important to document serum levels of luteinizing hormone (LH), FSH, estradiol (in girls) or testosterone (in boys), as well as conducting pelvic (girls) or testicular (boys) ultrasound and bone densitometry. Based on initial results, serum levels of luteinizing hormone, FSH, and gonadal steroids (estradiol or testosterone) should be obtained after gonadotropin-releasing hormone stimulation. For induction of puberty in boys, monthly intramuscular injection of testosterone is used, with a gradual increase to adult doses at the end of puberty. Unfortunately, side effects cannot be ignored, especially in males. In healthy men, testosterone in high doses might induce aggressive behavior and psychotic disorders, and the PWS population seems to be at greater risk. The initial dose in PWS patients should be one-third to one-half of the normally recommended androgen dose, with the objective of trying to prevent the aggressive behavior occasionally seen in some individuals. Larger prospectively controlled studies are still necessary in order to determine the impact of androgen replacement in this population. It is important to point out that psychologically, adolescence is a critical period in PWS, with psychotic episodes occurring in one-fifth of young adults; however, the worsening of temper tantrums or aggressive behavior were not confirmed in a study by Eiholzer et al.

In girls, conjugated estrogens or oral/transdermal estradiol are also used through a gradual increase. After 1–2 years of treatment, or if uterine bleeding occurs, progesterone is administered in association with estrogens in the last 10 days of the cycle. Attention should be drawn to the fact that estrogen replacement therapy is related to thrombotic events, and the risk of ischemic cerebrovascular disease in PWS is increased even in nonobese subjects. During adolescence, patients with greater cognitive impairment should always be supervised because of the risk of sexual abuse. The patients’ cognitive dysfunction, social and emotional immaturity, and the risk of Angelman syndrome in the offspring of PWS mothers contribute to advising against pregnancy among PSW patients. Mental retardation alone should not be a contraindication for allowing normal pubertal development to occur, or to preclude sex hormone replacement at any age in affected individuals. As adults, women with PWS have amenorrhea or oligomenorrhea, and infertility is the rule in both genders; however, there are reports of pregnancy in women with genetically documented PWS, while at the time of the preparation of this manuscript there were no reports about paternity.

Osteoporosis and bone density
Patients with PWS seem to have low BMD – probably due to growth hormone (GH) and sex steroid deficiencies – as well as low muscular activity. Adults with PWS present a high prevalence of osteoporosis. A study by Vestergaard et al evaluated the BMD and biochemical markers of bone turnover of eight patients with PWS (mean age of 24 years), and compared these markers with those of age-, sex- and BMI-matched controls. The results revealed that patients with PWS had lower whole-body BMD due to lower bone mineral content (BMC). The researchers also found that resorptive and formative bone markers were significantly elevated in PWS patients. In children, the bone mineral content is also reduced when compared with children with similar BMI. Rubin et al compared the body composition of twelve children (8–11 years) with PWS who were not GH-naive with that of obese and lean controls. The authors studied BMC, BMD, and the BMD z score for the patient’s total body, hips, and lumbar spine. The authors found significantly lower BMC and BMD in those with PWS compared to obese controls, but there were no differences between PWS and lean controls.

At the moment, there are no protocols for the prevention of osteoporosis in adolescents or adults with PWS, although with the use of rhGH from an early age and the improvement in muscular tone and physical activity, the body composition of these patients may improve not only by reducing the weight gain, but also by increasing their bone mass.

Hypothyroidism
Patients with PWS may develop hypothyroidism, both central and primary, congenital or acquired. Due to the clinical characteristics of PWS, the clinical diagnosis of hypothyroidism may be difficult. Therefore, it is important to periodically review the thyroid function by obtaining serum levels of thyroid-stimulating hormone, free T4, and total T4. Levothyroxine replacement therapy should be initiated as soon as hypothyroidism is diagnosed.

Adrenal insufficiency
Several studies point to an estimated mortality rate in PWS of 3% per year. Changes in the hypothalamic–pituitary–adrenal axis may be responsible, since under stress or aggravating factors, the adrenal response is inadequate or delayed in some patients. In 2008, de Lind van Wijngaarden et al investigated the hypothalamic–pituitary–adrenal axis in children with PWS using a single metyrapone dose as a stimulus, and the authors reported a high prevalence of central adrenal insufficiency in these patients. Other investigators using low- or high-dose adrenocorticotropic hormone stimulation tests or insulin tolerance tests found
a normal adrenal axis or a smaller prevalence of central adrenal insufficiency.\textsuperscript{57–59} 

At the moment, there are no data supporting the routine treatment of all PWS patients with glucocorticoid replacement doses. Treatment with hydrocortisone during stress should be provided to those who had no evidence of normal adrenal function. Maintenance therapy is performed only in patients with clinical symptoms of adrenal insufficiency.

## Short stature

Short stature is one of the capital characteristics of PWS. If they are left untreated, patients will reach an average adult height of 155 cm for males and 148 cm for females.\textsuperscript{50,61} Wollmann et al\textsuperscript{62} analyzed the growth pattern of 315 patients and found nearly normal growth in the first year, followed by decreased growth velocity, resulting that from 3 to 13 years old the 50th percentile of PWS growth chart is overlapped with the 3rd percentile of the growth chart of normal population. Furthermore, children with PWS have a subnormal pubertal growth spurt.\textsuperscript{63} It has been hypothesized that children with PWS have some degree of hypothalamic GH deficiency,\textsuperscript{63} which was demonstrated by studies that showed a blunted GH secretory pattern after pharmacological stimulus and low serum insulin-like growth factor-1 levels.\textsuperscript{64}

In addition, rhGH treatment has been approved by the United States Food and Drug Administration for PWS patients since 2000.\textsuperscript{65} A study conducted with 22 patients with PWS within the Kabi International Growth Study (KIGS) cohort found that the first year of rhGH treatment improved height from a median pretreatment of −1.6 standard deviation score (SDS) to −0.4 SDS, and that by the age of 18.1 years, patients had attained an adult height of −0.5 SDS for girls and −0.9 SDS for boys.\textsuperscript{66}

When compared to both normal-weight control subjects and BMI-matched nonsyndromic obese subjects, patients with PWS had reduced lean body mass, increased fat mass, and decreased BMC,\textsuperscript{67} all of which may also be exacerbated by GH insufficiency and hypogonadism. Besides restoring normal adult height, treatment with rhGH improves body composition by increasing muscle mass and decreasing body fat percentage, improving respiratory muscle function, physical strength, and agility.\textsuperscript{68} However, few long-term prospective studies have analyzed the rhGH effects over more than 2 years. Carrel et al\textsuperscript{68} investigated the effect of 4 years of rhGH. They first evaluated the 24-month response to rhGH therapy with a single regimen consisting of rhGH in doses of 1.0 mg/m\textsuperscript{2} Per day.\textsuperscript{68} During the next 24 months, patients were randomized to three different dosage regimens: 0.3 mg/m\textsuperscript{2} per day, 1.0 mg/m\textsuperscript{2} per day, and 1.5 mg/m\textsuperscript{2} per day.\textsuperscript{69} Their data showed that after 4 years of rhGH therapy, the early improvements in decreasing body fat and increasing lean body mass were attenuated by the low-dose regimen of 0.3 mg/m\textsuperscript{2} per day, and these results were increased by the high-dose regimen of 1.5 mg/m\textsuperscript{2} per day and were sustained by the medium-dose regimen of 1.0 mg/m\textsuperscript{2} per day, suggesting a positive dose–response effect.\textsuperscript{69} No major side effects were reported in the 4-year follow-up of this study.\textsuperscript{70} The metabolic effects of rhGH continue even after the discontinuation of the treatment. Coupaye et al\textsuperscript{70} compared patients who had received rhGH during childhood and adolescence (discontinued 7.0 ± 4.4 years prior to the study) with patients not treated with rhGH. They analyzed the body composition, insulin and glucose levels in nondiabetic patients, as well as and the diabetes control in patients with diabetes. The authors concluded that rhGH treatment in childhood and adolescence was associated with significantly decreased BMI, as well as with improved body composition and metabolic status in adults with PWS.\textsuperscript{70}

In addition, rhGH treatment induces cognitive changes as well. Some studies have demonstrated improvements in cognitive function.\textsuperscript{71–73} and one study demonstrated that in randomized controlled studies, rhGH prevents cognitive deterioration in patients who were not treated.\textsuperscript{71} In terms of motor performance, although physical training is of great importance, one review indicated that most studies showed that the use of rhGH facilitates the improvement of physical training in this population, decreasing any differences between PWS and the normal population.\textsuperscript{72}

Prior to the initialization of rhGH therapy, children with PWS must undergo a thorough clinical evaluation including anthropometric status (weight, height, BMI, waist circumference, and skinfold thickness); laboratorial assessment of metabolic status (glucose and lipid metabolism; hepatic enzymes, abdominal ultrasound; liver biopsy, if necessary); polysomnographic evaluation of sleep disorders; and spine X-ray for scoliosis appraisal.\textsuperscript{12,73} Bell et al\textsuperscript{74} reviewing the safety profile of rhGH in children (not specific to PWS children), reported possible adrenal insufficiency crisis events in patients after the start of rhGH treatment since all reported patients, except one who had idiopathic panhypopituitarism, had organic causes for GH deficiency. It should be noted that none of those patients had PWS.\textsuperscript{74} More data is required on the risk assessment of adrenal crisis induction after the initiation of treatment with rhGH in patients with PWS.
On a similar topic, an initial report suggested that rhGH could be worsening sleep apnea and could be leading to premature death of children with PWS receiving rhGH.75

Sleep disorders

Pathophysiology of sleep disordered breathing (SDB) in PWS seems to be multifactorial, including both peripheral and central mechanisms. Hypotonia, facial dysmorphism, and tonsillar hypertrophy may cause a reduction in the diameter of the upper airways; while fat deposition, respiratory muscle hypotonia, and kyphoscoliosis are related to ventilatory restrictive syndrome; and low response to partial pressure of CO₂ leads to central hypoventilation and hypercarbia.76 Even nonobese patients are at an increased risk of developing SDB, and some issues such as central apnea may be present as early as during the first year of life.77,78 Sudden death, especially during sleep, has been widely reported as one of the major causes of death in PWS.8,53,79–81 Most of the deaths were related to respiratory problems like respiratory tract infection, adenoid and tonsil hypertrophy, and sleep apnea.

Seventy percent of PWS patients present some degree of SBD.82 Obstructive sleep apnea (OSA) is a primary disorder, and is considered a minor criterion for the diagnosis of PWS.83 OSA may lead to cardiovascular complications, such as systemic arterial hypertension and cor pulmonale, with increased severity and a high impact on morbidmortality.12 In PWS patients, OSA may also be related to autistic behavior and impulsivity.85 Excessive daytime sleepiness and rapid eye movement sleep abnormalities are common issues in PWS and can be considered primary disorders, although OSA may aggravate them.12 DeMarcoantonio et al84 retrospectively evaluated the need for tonsillectomy in PWS patients with OSA. Despite symptomatic improvements associated with a lower apnea/hypopnea index (16.4 versus 4.4, respectively before and after surgery), the difference did not reach statistical significance, possibly because of the small number of cases analyzed.84

rhGH and sleep disorders

It has been suggested that rhGH therapy might aggravate tonsillar hypertrophy, resulting in a worsening of OSA, which would be responsible for the emergence of sudden death.76–80 A series of studies have been published with the purpose of establishing the relationship between rhGH treatment and breathing disorders.76–80 However, two prospective studies pointed to improvements in response to the partial pressure of CO₂ in ventilation patterns at rest, in upper airway obstruction, and in accessory respiratory muscle tonus throughout the treatment.85,86

Regarding the apnea–hypopnea index, two other studies described improvement on sleep abnormalities in overnight polysomnography after 6 months of rhGH therapy, but without reaching statistical significance.87,88 Nonetheless, some patients had obstructive symptoms and the OSA worsened, which was mostly attributed to upper airway infections, tonsillar hypertrophy, and high levels of insulin-like growth factor-1.77 The initial worsening was not confirmed in some patients after a follow-up polysomnography. Although safety issues have been raised after case reports of worsening OSA during rhGH treatment have been reported.76,80,89 and following improvement of obstructive symptoms after withdrawal of the therapy,90 prospective studies with larger cohorts have failed to show an increased mortality risk.77,90 In fact, one nocturnal sudden death was observed in studies by both Festen et al17 (out of 53 patients) and de Lind van Wijngaarden et al90 (out of 55 patients), and both of the patients had previous, near normal polysomnography.

The effect of rhGH in young children with PWS was investigated in a prospective clinical case series study.91 Sixteen patients with a median age of 16 months at enrollment were followed. The authors concluded that rhGH improved arterial oxygenation and cardiovascular function during sleep.91 In the February 2013 issue of The Journal of Pediatrics, Al-Saleh et al92 presented the follow-up data of 15 children with PWS before and up to 2 years after starting rhGH. While two patients had to discontinue rhGH due to respiratory problems, the authors concluded that if there are no signs of SDB before and 6 weeks after the initiation of rhGH, the risk of developing SDB after that is small.92 In one of the editorials, Whitman and Myers reviewed the published data and stated that:

Although sleep disordered breathing is essentially ubiquitous in the population with PWS, there is little evidence that initiating rhGH increases that risk in most patients. Nonetheless, in some patients there does appear to be an increased risk of obstructive events.93

Thus, given the high prevalence of SDB in patients with PWS, it is recommended that polysomnography be performed, especially for the investigation of OSA, regardless of symptoms and indication of rhGH treatment. The evaluation of ear, nose, and throat should be requested whenever needed.12 In addition, if rhGH therapy is instituted, polysomnography should be performed before and during treatment, so as to detect a possible worsening of the obstructive pattern. Since most of the deaths in patients receiving rhGH occurred in the first months...
of therapy, the initial rhGH dose should be one-fourth to one-third of the maintenance dose, and over a period of months, the dose should be slowly increased to full maintenance. In severe cases of obesity or obstructive symptoms, the focus should be aimed at improving complications before recommending hormone therapy.

Conclusion
PWS patients have increased mortality due to their hypothalamic dysfunction causing hypoventilation, hypotonia, and obesity. The main goal in the follow-up of these children is to improve motor function and prevent obesity. Supporting and orienting their caregivers is of utmost importance. Controlling patients’ weight gain (which is insufficient in the first year of life, and becomes excessive after infancy) requires tremendous effort. The use of rhGH helps in several aspects, although it has to be done under strict surveillance.

As we improve their motor skills in infancy and decrease the patients’ weight gain, we can provide them with improved quality of life throughout their prolonged lifespan.

Disclosure
The authors report no conflicts of interest in this work.

References


