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Growth Hormone Therapy in Children with Prader-Willi Syndrome

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Prader-Willi syndrome is a complicated genetic disorder caused by a mutation on chromosome 15q11-13. The disease results in morbid obesity due to hyperphagia, growth disturbance, multiple endocrine problems from hypopituitarism, developmental delay, and cognitive or behavioral problems. Recombinant human growth hormone has been used to improve body composition and muscle mass, which plays a main role in treating patients with Prader-Willi syndrome. We describe previous studies showing the efficacy and safety of growth hormone treatment in children with Prader-Willi syndrome and provide treatment guidelines. Growth hormone therapy could be beneficial for children with Prader-Willi syndrome and improve their quality of life.

Keywords: Prader-Willi syndrome, Growth hormone, Growth hormone deficiency, Guideline

Introduction

Prader-Willi syndrome (PWS) is a complicated genetic disorder with endocrine and neurologic symptoms, which is considered the most common genetic cause of obesity. The frequency of PWS has been reported as 1:10,000 to 1:30,000 live births without gender differences[1]. PWS is mostly caused by deletions on paternal alleles or maternal uniparental disomy (UPD) on chromosome 15q11-13. The features of this disease include infantile hypotonia, failure to thrive in early life with hyperphagia, and severe obesity in later life. Individuals with this disease exhibit mental retardation, hypogonadism/hypogenitalism, cognitive and behavioral problems (tantrums, compulsions, compulsive skin picking), and hypothalamic dysfunction including growth hormone (GH) deficiency. A short stature is usually presented in the second decade of childhood in the absence of GH replacement and lack of a pubertal growth spurt. The entire pathogenesis of hypothalamic dysfunction, especially GH deficiency (GHD), remains unclear. No medications are currently known to aid in controlling hyperphagia, a prominent cause of severe obesity in PWS[2]. Recombinant human GH replacement is the conventional treatment to improve the quality of life of patients with PWS; however, there are some safety issues. Here, we present a summary of previous studies on the efficacy and safety of GH treatment in children with PWS and provide treatment guidelines.

Efficacy and Safety of GH Therapy in PWS Children

GH treatment was approved by the Food and Drug Administration for children genetically confirmed with PWS in 2000. Subsequently, it was approved in South Korea in 2005. Hypothalamic dysfunction and hypopituitarism are mainly observed in PWS, which can induce a short stature and hyperphagia. PWS is characterized by the dysregulation of the GH/insulin-like growth factor I (IGF-1) axis due to a complex hypothalamic involvement. Unlike patients with overnutrition who have high-normal IGF-I levels, IGF-I levels in children with PWS are in the low or low-normal range[3]. PWS is frequently accompanied by GHD, which is the most frequent endocrinopathy in PWS, especially in cases of UPD[4]. According to previous studies, the prevalence of GHD

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in PWS is 45–80% depending on the database and diagnostic criteria used[5,6]. PWS shares some characteristics with GHD, including reduced muscle strength, altered body composition, low energy expenditure, and reduced growth even in the presence of obesity. GH treatment may also be effective in children with PWS by increasing body fat, reducing lean mass, reducing muscle strength, reducing bone mineral density, and alleviating psychological disorders. Generally, GH replacement is considered as the standard treatment for children with PWS, and abundant evidence supports its beneficial effects on the quality of life of patients.

1. Effects on body composition

The positive effect of GH treatment on body composition is well established. In infants with PWS, GH replacement-related improvements in head circumference, height, body mass index (BMI), body composition (improvement in lean muscle mass and delay of fat tissue accumulation), and body proportion have been reported[7,8]. Previous long-term studies showed GH replacement normalized the final height more than 2 standard deviation scores (SDS)[3,9]. In another study, the baseline hand, foot, tibia length, and arm span SDS were assessed, and they were significantly increased by GH treatment; however, these indices remained below 0 SDS in PWS children for 4 years during GH treatment[10].

In a 5-year randomized controlled trial conducted by Lindgren et al., among 18 PWS prepubertal patients, BMI SDS significantly decreased from 3.0 to 1.5 SDS in the group treated with a dose of 0.1 IU/kg/day for two years of GH treatment, and from 2.8 to 1.2 SDS in the group treated with a dose of 0.2 IU/kg/day from second year[3]. The BMI in both groups was increased during a 6-month period without treatment, and following the restart of GH therapy, BMI SDS were stabilized. Fasting insulin, glucose, and the A1c fraction of glycosylated hemoglobin remained within normal ranges during the 5 years of GH treatment. Another randomized controlled trial of GH treatment in children with PWS reported similar results, showing that GH improved body composition and muscle mass, and there was no deterioration of metabolic parameters including fasting glucose, insulin, and low-density lipoprotein cholesterol[11].

2. Effects on motor performance and quality of life

PWS children have severe muscular hypotonia, a weak cry, and poor sucking reflex during infancy, which can result in motor development delay and a lower quality of life. Motor dysfunction becomes more noticeable with age. Several studies demonstrated that GH treatment could support the motor development of children with PWS. Corripio et al. reported that children started walking earlier when GH treatment was initiated before 15 months of age compared with after 15 months of age[12]. In a randomized controlled study, GH treatment enhanced motor benefits induced by physical training[13]. Lafortuna et al. reported GH treatment gradually increased the handgrip strength, peak torque of knee extension extrapolated at zero angular velocity, and exercise endurance before exhaustion of patients with PWS[14]. Interestingly, the beneficial effects of GH treatment on muscle strength and motor flexibility were found to be independent of GH deficiency in PWS subjects[8]. In another study, most patients had improved psychological well-being[15]. GH treatment is essential for motor development in children with PWS so that they can develop as normally as possible.

3. Effects on behavioral and cognitive impairment

PWS patients have intellectual disabilities as well as behavioral problems such as social impairment and compulsive behavior. There is little information on the effectiveness of GH treatment for behavioral problems in PWS patients. Some studies reported that PWS patients undergoing GH treatment showed fewer behavioral problems[16,17]. Another long-term study on GH treatment reported that there was no improvement but also no deterioration of behavioral problems in children with PWS[18]. Nevertheless, it seems that GH could have a marked effect on cognition. There is strong evidence indicating that long-term GH treatment is beneficial for the intelligence quotient (IQ) and cognition[8]. Lo et al. reported that verbal IQs, composite IQs, adaptive communication capability, and daily living skills were significantly higher in the GH treatment group than in the untreated group[16].

4. Adverse effects and safety concerns

Even if GH treatment is well-tolerated in most PWS patients, there are still safety concerns. Scoliosis is a possible adverse effect of GH treatment in children. Usually, PWS patients show a high rate of scoliosis, and they have fragile bones and low muscle strength. GH treatment plays a beneficial role in muscle strengthening, and it may help alleviate scoliosis. In controlled studies comparing GH-treated and non-treated children with PWS over a 6-year time frame, there was no difference in the rate of de-

Table 1. Evaluation of patients with Prader-Willi syndrome before growth hormone treatment

Evaluation	Interventions
Physical examination	Height, BMI, abdominal circumference, head circumference, pubertal status
Endocrine evaluation	TFT, IGF-1, IGFBP-3, bone age x-ray, HbA1c, fasting insulin/glucose, OGTT, fasting total cholesterol, TG, LDL/HDL-cholesterol, AST, ALT, abdominal US, morning cortisol/ACTH
Body composition	DEXA
Sleep study	Polysomnography or ENT examination with sleep oximetry
Scoliosis evaluation	Spine x-ray
Nutritional evaluation	Feeding habit
Respiratory evaluation	ENT examination with laryngoscopy

GH stimulation testing is not recommended in the pediatric age.
BMI, body mass index; TFT, thyroid function test; OGTT, oral glucose tolerance test; TG, triglyceride; US, ultrasonography; AST, aspartate transaminase; ALT, alanine aminotransferase; DEXA, dual energy x-ray absorptiometry.

velopment or severity of scoliosis between groups[11,19]. Another concern of GH treatment is metabolic disorders. An increase in insulin resistance is suspected with GH treatment. However, a comparison of long-term GH-treated and non-treated school-aged children with PWS showed no evidence of significantly higher fasting insulin, glucose, or homeostatic model assessment-insulin resistance (HOMA-IR) levels attributable to GH treatment[11].

Some studies reported that the death of patients with PWS might be correlated to GH treatment[20-22]. However, PWS patients who died had diabetes mellitus, metabolic syndrome, sleep apnea, pre-existing respiratory infection, or cardiac disorders with or without morbid obesity. These morbidities may not seem to be exacerbated by GH treatment[23,24]. If patients have any of these morbidities, GH treatment should be carefully considered.

Guidelines for GH Therapy in PWS Children[25]

After genetic confirmation of the diagnosis of PWS, GH treatment should be considered, and if initiated, should be continued for as long as the benefits outweigh the risks. GH stimulation testing should not be required as part of the therapeutic decision-making process for infants and children with PWS. The selection of patients with PWS for GH therapy and dosing strategy should not depend on the genetic class of PWS.

Early intervention is recommended for patients with PWS (as early as 4 to 6 months old)[25,26]; however, some experts are currently starting treatment from as early as 3 months old. No consensus reached on the age of GH start. All experts agreed the benefits of treatment before the onset of obesity, which often begins by 2 years of age. Studies thus far have indicated that no age is too early for GH treatment, and the sooner it is started, the more benefit it has.[26]

Before the initiation of GH therapy, patients with PWS should have a genetically confirmed diagnosis and received expert multidisciplinary evaluation including polysomnography to detect obstructive apnea during sleep, which can result in sudden death. The evaluation of patients includes the assessment of weight, height, BMI, waist circumference, pubertal status, additional endocrine deficiencies (thyroid function test (TFT), IGF-1 level, bone age), and scoliosis (Table 1). A sleep study is recommended before the initiation of GH therapy to assess for and treat obstructive apnea[26].

Exclusion criteria for starting GH treatment in patients with PWS include severe obesity (over 95 percentiles of BMI for age), uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, and active psychosis. GH therapy should not be initiated during an acute respiratory infection and should not be interrupted during subsequent episodes of respiratory infection unless the onset of breathing difficulties is indicated. Scoliosis should not be considered as a contraindication to GH treatment in patients with PWS.

Treatment for infants and children with PWS should start with a daily dose of 0.5 mg/m^2/day subcutaneously with subsequent adjustments toward 1.0 mg/m^2/day every 3–6 months according to the clinical response, guided by the maintenance of physiological levels of IGF-1. Subsequent dosage titration should be based on the clinical response and age- and sex- appropriate IGF-1 levels in the range of 1 to 2 SDS (upper part of the normal range, maximum 2 SDS, for healthy, age-matched normal individuals).

During GH treatment, monitoring patients with PWS should clarify the specific benefits and risks of treatment in this population and identify the potential impact of other hormonal deficiencies. Patients with PWS must be followed carefully for po-

Table 2. Evaluation of patients with Prader-Willi syndrome during growth hormone treatment

Evaluation	Interventions	Interval
Interview	Compliance, sleep habit, feeding habit	At every visit
Physical examination	Height, weight, BMI, abdominal circumference, head circumference, pubertal status	3–6 months
Endocrine evaluation	TFT, IGF-1, IGFBP-3, bone age x-ray, HbA1c, fasting insulin/glucose, OGTT, fasting total cholesterol, TG, LDL-cholesterol, HDL-cholesterol AST, ALT, abdominal US, morning cortisol/ACTH	3–6 months
Body composition	DEXA	6–12 months
Scoliosis evaluation	Spine x-ray	6–12 months
Sleep study	ENT assessment, polysomnography	Development or worsening
Respiratory evaluation	Respiratory clinical tests	At each event

BMI, body mass index; TFT, thyroid function test; OGTT, oral glucose tolerance test; TG, triglyceride; US, ultrasonography; AST, aspartate transaminase; ALT, alanine aminotransferase; DEXA, dual energy x-ray absorptiometry.

tential adverse effects during GH treatment. Every 3–6 months, height, weight, BMI, pubertal status, scoliosis, IGF-1, and side effects should be evaluated. Body composition should be examined every 6–12 months by waist circumference, skinfold thickness, or dual energy x-ray absorptiometry (DEXA) measurements. ENT assessment and sleep oximetry or polysomnography should be performed within the first 3–6 months. If the patient shows the development or worsening of sleep-disordered breathing, snoring, or enlargement of tonsils and adenoids, it is important to perform ENT examinations. Fasting glucose, insulin, and hemoglobin A1c levels should be evaluated if the patient is obese and/or older than 12 years old and/or has acanthosis nigricans and/or a familial history of diabetes (Table 2).

Patients undergoing GH treatment should be monitored for potential side effects including sleep apnea, disordered breathing, or insulin resistance indicated by high fasting insulin levels. Other side effects could include hypothyroidism, scoliosis, joint pain, or slipped capital femoral epiphysis. If there is a marked deterioration in behavior with or without overt psychiatric symptoms, a psychiatric assessment is needed. GH treatment is usually well-tolerated in PWS patients with behavioral problems. Early cessation is lower than in other GH-treated patients with conditions such as idiopathic short stature or Turner syndrome and children who are born small for gestational age (SGA)[6]. GH retesting after achievement of the final height should be considered for all PWS patients[27]. In addition, whether genotype-phenotype correlations may be linked to specific outcomes related to GH treatment should be further examined.

Conclusion

In PWS children, GH replacement could contribute to improvements in head circumference, height, BMI, body composition (improvement in lean muscle mass and delay of fat tissue accumulation), body proportion, muscle thickness, acquisition of gross motor skills, language acquisition, and cognitive scores. Early intervention appears to be more beneficial for children with PWS. Some studies have been reported improvements in behavior with GH treatment in older children and adolescents, but controversy still exists. Considering the safety issues of GH treatment, specific guidelines should be followed to minimize the risk of death among children with PWS.

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