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Growth Hormone Therapy in Adults with Prader-Willi Syndrome

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Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder characterized by hypothalamic-pituitary dysfunction. Many features of PWS indicate a deficiency in growth hormone (GH) production, and these findings provide a rationale for GH therapy in PWS. It is possible that rhGH therapy could have beneficial effects in adults with PWS, similar to those in adults with GH deficiency (GHD) of non-syndromic cause. However, there is a paucity of data on the use of GH in adults with PWS. Here, the previous studies about efficacy and safety of rhGH therapy in PWS adults are summarized. Briefly, rhGH therapy in PWS adults may improve body composition, leading to increased lean body mass and decreased fat mass, as well as decreased subcutaneous and visceral adiposity without overall changes in body mass index. There may be at least transient deterioration in glucose homoeostasis in some PWS patients on rhGH therapy, which requires further study. In addition, clinical care guidelines for rhGH therapy in adults with PWS were suggested.

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

Introduction

Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder characterized by hypothalamic-pituitary dysfunction[1,2]. The main clinical features consist of neonatal hypotonia, distinctive facial features, delayed overall development with mental deficiency, behavioral abnormalities, poor growth in infancy followed by overeating with severe obesity, short stature, and hypogonadism[3]. Many features of PWS indicate a deficiency in growth hormone (GH) production, including low growth velocity despite obesity, reduced lean body mass, low insulin-like growth factor-I (IGF-I) levels, and low insulin levels[4,5]. These findings provide a rationale for GH therapy in PWS. The Food and Drug Administration approved treatment in children genetically confirmed with PWS in 2000 without prior laboratory determination of GH deficiency (GHD). GH treatment is now commonly prescribed in infancy and childhood to increase stature in PWS cases, but also increases muscle and decrease fat, thereby lowering risk factors for diabetes and cardiopulmonary problems. Increased alertness, physical activity, and self-esteem in older children are potential effects of GH treatment[6-10], which should improve the quality of life in adulthood. In addition, Lindgren and Lindberg[11] documented that GH treatment in children with PWS appears to normalize them to an adult height with improvement in body composition, an important outcome for individuals with this disorder. Early GH therapy during the first two years may improve neurodevelopment, increase muscle mass, and reduce obesity in PWS infants[12]. It is possible that rhGH therapy could have beneficial effects in adults with PWS, similar to those in adults with GHD of non-syndromic cause. However, there is also concern about potential risks of this therapy, as rhGH has anti-insulin effects and might impair respiratory function in children with underlying sleep apnea, which is frequently present in patients with PWS[13,14]. However, there is a paucity of data on the use of GH in adults with PWS; existing studies have small in scope, suggesting that the findings of individual studies may be difficult to extrapolate to the population of adult patients with PWS at large. Here, the previous studies about efficacy and safety of rhGH therapy in

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PWS adults are summarized and a brief guideline is suggested.

1. Clinical studies investigating the efficacy and safety of rhGH therapy in PWS adults

A meta-analysis of eight studies examining the effects of rhGH therapy included 134 PWS adults (75 men, 59 women)[15]. All studies had prospective design, but only two were randomized placebo controlled. All the patients fulfilled Holm's diagnostic criteria for PWS, and the syndrome was genetically verified in 128 (95.5%) patients. Five studies and three studies reported on patients with PWS who received 12 months and 24–72 months of GH treatment, respectively. Mean age for study participants ranged between 25 and 30.5 years (mean±SD 28.3±3.5 years), and 53% were women. Subjects' mean BMIs ranged between 27.4 and 46.3 kg/m^2, and 59% had confirmed GHD. All studies required at least 1 year without prior rhGH treatment in patients who had previously received this therapy (13/51). Fifteen patients (11.7%) were diabetic at baseline. Hypogonadism was a common finding in patients of both genders, and 38 patients were noted to have had stable sex hormone replacement during the studies. Mean rhGH treatment dose ranged between 0.53 and 0.96 mg/day at 12 months and 0.35 and 0.61 mg/day in studies of longer duration. In most studies, rhGH dose was titrated based on serum IGF1 levels. Nutrition counselling was provided in all studies, and patients were advised to avoid changes in diet during therapy. Body composition was estimated by DXA. One study additionally assessed total body water by bioelectrical impedance. Visceral and subcutaneous adipose tissue area was measured by computerized tomography. Thigh fat mass and muscle mass were measured in one study. Five studies performed standard 75 g oral glucose tolerance tests (OGTT)[16-20].

1) Efficacy end-points (12-month data)

There was a significant decrease in body fat (including per cent fat mass and visceral and subcutaneous adiposity) and a significant increase in lean body mass (LBM) on rhGH therapy. There were no significant changes in BMI, weight circumference (WC), weight hip ratio (WHR), systolic BP, and diastolic BP on rhGH therapy. Serum IGF-1 was significantly increased after 12 months of rhGH treatment. There was a small, but statistically significant, increase in fasting plasma glucose (FPG) as well as a trend towards higher fasting insulin and HOMA values on rhGH therapy without change in HbA1c. There were no significant changes in lipid profile (total, LDL, and HDL cholesterol and triglycerides) after 12 months of rhGH therapy.

2) Safety end-points (12-month data)

There were no study-related deaths reported. One patient with diabetes mellitus withdrew because of worsening glycemic control, and 12 patients developed impaired glucose tolerance after 12 months of rhGH therapy. However, no patient was diagnosed with diabetes mellitus during rhGH therapy. The most common side effect reported was edema, reported in 20 of the 134 patients. Other side effects, besides changes on glucose homoeostasis, were myalgia (one patient) and headache (one patient).

3) Long-term data (24–72-month data)

Three studies reported on patients with PWS who received 24–72 months of rhGH treatment. There was a decrease in fat mass (per cent body fat) and an increase in LBM on rhGH therapy without significant change in BMI. As anticipated, there was a significant increase in serum IGF-1 in response to rhGH administration. There were no changes in FPG, HbA1c, or HOMA. In the study by Hoybye et al[16], two patients died of long-standing cardiac failure, including one patient on rhGH therapy and one control subject. No patient on rhGH treatment developed impaired glucose tolerance or overt diabetes mellitus. In the study by Crugni et al. (presented in abstract form), two of six patients developed impaired glucose tolerance but none developed diabetes mellitus after 72 months of rhGH therapy. In the study by Sode-Carlsen et al., one patient with pre-existing diabetes mellitus was withdrawn because of deterioration in glycemia; five normoglycemic patients developed impaired glucose tolerance; and three patients with impaired glucose tolerance at baseline developed diabetes mellitus during rhGH therapy for 24 months[18]. In the same study, three patients with impaired glycemic tolerance at baseline became normoglycemic during rhGH therapy[18].

4) Exercise capacity

Changes in exercise capacity in response to rhGH therapy were examined in two studies[17,21]. Sode-Carlsen et al.[17] performed a 10-metre walk test and found improvement (faster walking) in 6/18 rhGH-treated patients, but also in 2/16 control patients, and a repeat standing test in which 6/18 rhGH-treated and 4/16 controls had poorer scores compared with baseline. Gondoni et al.[21] used treadmill exercise testing and reported an increase of 19% in exercise capacity (in metabolic equivalents) after 12 months of rhGH treatment (P<0.001).

5) Neuropsychological tests

Hoybye et al.[22] performed a battery of neuropsychological tests using specific questionnaires and found improvement in cogni-

tive and motor performance tests during rhGH therapy, with deterioration in physical and social status and overall functioning after rhGH treatment was discontinued.

6) Behavioral assessments

Mogul et al.[20] reported a beneficial reduction in total symptom score on behavioral assessments by family and study aides (from 8.3±4.7 at baseline to 6.13±4.5 after rhGH therapy, $P<0.05$).

7) Quality of life

Bertella et al.[23] evaluated quality of life by physical and psychological well-being questionnaires (SF 36) self-administered by the patients or their caregivers. They found significant improvements in both scales, with greater improvements noted in patient questionnaires than in questionnaires completed by their caregivers. As all these studies were open label, so data on cognitive function and psychological well-being must be viewed with caution.

8) Cardiac function

Marzullo et al.[24] examined the effects of rhGH treatment on cardiac function, assessed by echocardiography and cardiac scintigraphy. Their results showed an increase in left ventricular mass in 61% of rhGH-treated patients and a mild decrease in left ventricle ejection fraction on echocardiography, which was of borderline statistical significance. The latter finding was not demonstrated on cardiac scintigraphy in the same prospective (uncontrolled) study.

9) Pulmonary function

No changes in pulmonary function were reported by Sode-Carlsen et al.[17], using peak expiratory flow in response to 12 months of rhGH therapy. In the same controlled study, there was a statistically non-significant increase in total body water in rhGH subjects, assessed by bioimpedance.

10) Obstructive sleep apnea

Potential concern has been a possible negative effect of rhGH treatment on obstructive sleep apnea. Several fatalities have been reported in pediatric patients with PWS after starting rhGH therapy[25]. Sleep apnea occurs in 50–100% of PWS patients and is usually mild, but may be exacerbated by rhGH therapy as a result of hypertrophy of tonsillar tissue and tissue oedema caused by sodium retention[14,26,27]. Only one study of relatively short duration examined sleep-related breathing in a cohort of patients with PWS. In this study by Miller et al.[13], sleep-related breathing was investigated in a population of children (n=15) and adults (n=10) with PWS at 6 weeks after beginning rhGH treatment. Among adult patients, there was a decrease in apnea/hypopnea index (–7.58±9.0, $P<0.05$) and a trend towards an improvement in central apnea/hypopnea index (–3.42±4.94, $P=0.056$). Titrating rhGH treatment on the basis of serum IGF-1 may help to minimize adverse effects. Additional studies are needed to fully elucidate the effects of rhGH therapy on sleep-related breathing and glucose homoeostasis in PWS adults.

2. Clinical care guidelines for rhGH therapy in adults with PWS

Adults with PWS should have an evaluation of the GH/IGF axis before rhGH treatment. Adults with PWS should receive a starting dose of 0.1–0.2 mg/d based on age, presence of edema, prior rhGH exposure, and sensitivity, and concomitant oral estrogen use. Subsequent dosage titration should be based on clinical response, age-, and sex-appropriate IGF-I levels in the 0 to 2 SDS range. Exclusion criteria for starting rhGH in patients with PWS include severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, and active psychosis. Scoliosis should not be considered a contraindication to rhGH treatment in patients with PWS. Polysomnography should be per-

Table 1. Evaluation before starting rhGH treatment

Evaluation	Testing/interventions
Weight, height, BMI	
Waist circumference	
Additional endocrine deficiencies	FT4, TSH, IGF-I
	GH provocation test
	HbA1c, fasting insulin/glucose, OGTT
	Fasting total cholesterol, TG, LDL-HDL-cholesterol
	AST, ALT, Abdominal US
	DEXA
	Adrenal function
Referral to dietician	Nutritional evaluation and advice
Sleep-disordered breathing	Tonsillectomy, adenoidectomy
Referral to pneumologist/ sleep clinic	Polysomnographic evaluation
Scoliosis evaluation	Spine x-ray

BMI, body mass index; OGTT, oral glucose tolerance test; DEXA, dual energy X-ray absorptiometry; GH, growth hormone; TG, triglyceride; US, ultrasonography.

formed before starting therapy. Evaluation before starting rhGH treatment is shown in Table 1.

3. Further research regarding rhGH use for PWS is suggested as follows

1) Effects of rhGH therapy in adults with PWS on behavior and cognitive function, activities of daily living and well-being, quality of life, bone mineral density, and muscle function.

2) Effect of rhGH in adults with PWS on glucose metabolism/diabetes risk, sleep and sleep-disordered breathing, and cardiovascular risk.

3) Long-term post-treatment effects of rhGH on mortality and morbidity.

4) The optimal dosage of rhGH treatment.

5) Impact of rhGH treatment on Influence of IGF-I titration on clinical effects.

6) Randomized clinical trials investigating combination approaches to treatment.

7) Cost/benefit analysis of this expensive treatment.

Conclusion

rhGH therapy in PWS adults may improve body composition, leading to increased lean body mass and decreased fat mass, as well as decreased subcutaneous and visceral adiposity without overall changes in body mass index. There may be at least transient deterioration in glucose homoeostasis in some PWS patients on rhGH therapy, which requires further study. Data is lacking on bone mineral density, muscle function, energy expenditure, physical activity, behavioral and cognitive status, and quality of life. Larger studies of longer duration using a blinded, placebo-controlled designs are needed to clarify these issues.

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