Growth Hormone Treatment in Prader-Willi Syndrome

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Prader-Willi syndrome (PWS) is a congenital disease that was initially described by Prader, Willi and Labhart in 1956.[1] PWS affects one in 10,000 to 15,000 children.[2] It is speculated that PWS affects many parts of the body. Infants with PWS demonstrate poor weight gain, and hypotonia associated with poor sucking, compromised respiratory function, early Failure To Thrive(FTT), and delayed motor development skills.[1] Other symptoms may include almond-shaped eyes, scoliosis, narrow bifrontal skull and very small hands and feet in comparison to child's body.[3] Intense craving for food and hyperphagia is an important characteristic of early childhood PWS that may lead to excessive intake which can result in uncontrollable weight gain, abnormal body composition with increased fat mass, and reduced muscle tone and lean body mass.[1] Morbid obesity may lead to type 2 diabetes, high blood pressure, and joint and lung problems.[3] Several complications attributed to PWS persist during adulthood including decreased Growth Hormone (GH) and IGF-I secretion, diminished bone mineral density, reduced mental ability, hypogonadism, short stature, sleep disorder and temperature instability. Some signs of PWS may be present at birth such as undescended testicles in male infants.[3,4]

Some studies suggest that lack of genetic expression on chromosome 15 is the main cause of PWS. Research indicates that lack of expression can be caused due to a deletion or maternal disomy. In rare cases translocation is also considered a contributing factor for gene defect in PWS.[4] The imprinted 15q11-q13 chromosome region includes DNA that is normally active on the father's chromosome 15 and inactive on the chromosome 15 inherited from the mother. About 70 % cases of PWS occur when a segment of the paternal chromosome 15 is deleted. In another 25 % of cases, both chromosome 15s are inherited from the mother and

no chromosome 15 is present from the father. This is called maternal uniparental disomy. The missing paternal chromosome 15 that contains the active genes required for normal development contributes to PWS in individuals with inheriting both maternal chromosome 15s. Since the genetic changes occur randomly, many patients do not have a family history of the condition. [3,4]

Hypothalamic dysfunction also contributes to the features of PWS. Numerous symptoms suggest decreased GH secretion in both children and adults with PWS. GH is produced by the pituitary gland to fuel childhood growth and help maintain tissues and organs system. GH acts on the liver and other tissues to stimulate production of insulin-like growth factor I (IGF-I), which is responsible for the growth-promoting effects of GH. Growth Hormone has several metabolic effects. Growth promotion is one of the major effect of GH on metabolism. GH has a glucose sparing effect as it decreases glucose uptake by muscles. GH also plays an important role in protein synthesis and synthesis of DNA and RNA. In addition, lipolysis is considered a significant characteristic of GH as it breakdowns the fatty acids in blood.[5]

PWS patients treated with GH often positively respond to the treatment. To date several studies have speculated the effectiveness of the use of GH on children and adults. GH is an approved medication by Food and Drug Administration for long term treatment of children with growth failure due to PWS in the United States.[6] Many studies hypothesize the benefits associated with short and long term use of GH on children and adults. Short term GH therapy has indicated improvement of body composition and lean body mass. It has also shown improvement in height-for-age, psychomotor and psychological development and benefits in

children. The use of growth hormone before the onset of puberty may also contribute to a normal height in adulthood.[4]

Several studies in the Scandinavian countries, the Netherlands, France and the United States followed patients with PWS under GH therapy. These studies mainly investigated the effects of short term and long term use of GH on children and adults with PWS. The studies reported improvements and documented physical changes that indicate the effectiveness of the use of GH therapy for patients with PWS.

As mentioned earlier increased fat mass is a general characteristic of PWS. Studies suggest a significant decrease in body fat after the administration of GH therapy in different stages of life. The Scandinavian multicenter placebo control trial, a study performed in Scandinavian countries, reported that 12 months of GH therapy resulted in a decrease in fat mass and increase in lean Body mass in adults.[2] A follow up study of the Scandinavian trial revealed similar results confirming the short term and long-term GH findings in adults who were followed for two years.[7] US Adult Prader-Willi Syndrome Study, a small scale open label multicenter trial, demonstrated that GH administration for 12 months improves Lean Body Mass (LBM) and decreases fat percentage in adults.[6]A Dutch multicenter prospective trial, reported consistent results of decreased fat mass and improved lean body mass with four years of GH therapy in children.[4] An early treatment cohort study demonstrated the beneficial effects of early GH treatment in infancy confirming reduction in body fat and improved muscle strength in children.[1]

Lubna Qureshi
NTDT 5340
December 7, 2012

IGF-I plays an important role in childhood growth and continues to have anabolic effects in adults. GH plays a major role in synthesis of IGF-I. GH deficient children with PWS are reported to have low IGF-I values. A retrospective study in France compared changes in serum IGF-I, IGF binding protein 3 (IGFBP-3), IGF-I to IGFBP-3 molar ratio, and growth velocity during the first 2 yr of GH therapy in children with PWS and GH deficiency (GHD). Data reveled that GH treatment elevated the IGF-I levels more in children with PWS than in GHD.[8] A variety of studies exhibit consistent findings attesting to the beneficial effects of GH therapy. Research performed through different stages of life also favors the generalization of results.

The early treatment cohort study assessed the impact of GH therapy begun early in life on the natural history of PWS.[1] A total of forty-eight children with PWS were studied. Twenty one subjects, aged 6 to 9 years, who had been treated with GH at 1mg/m^2/d for 6 years beginning at age 4 to32 months, were compared with 27 children aged 5-9 years prior to treatment with GH. Comparisons were made for percent body fat, lean body mass, carbohydrate/lipid metabolism, and motor strength. When compared with the PWS children not treated with GH, children treated with GH early in life demonstrated 8.5% decrease in body fat, 14mg/dl higher HDL, 31mg/dl lower LDL and 16 cm increase in height. The study revealed that GH treatment in children with PWS, begun prior to 2 years of age, improves body composition, motor function, height, and lipid profiles. The extent of these findings suggests that long-term GH therapy during infancy favorably alters the natural history of PWS by reducing body fat, improving muscle strength and lipid profiles without adverse effects favoring consideration for initiation during infancy.[1]

Lubna Qureshi
NTDT 5340
December 7, 2012

The Dutch multicenter prospective trial followed 59 pre-pubertal children, age 5.9-$^{+}$ 3.2 years, with continuous 1mg/m^2/d GH treatment for 4years. Children received a dose of 0.5mg/m^2/d during the first four weeks of the treatment. Dose was adjusted according to the body surface area every three months when the children visited the facility. Dietary counseling was provided to children and parents. Physical therapy administered prior to the treatment was continued in addition to the physical activity performed at schools. Results showed a decrease in fat % and improvement in LBM, height and head circumference after four years of GH treatment. No significant change was noticed in total cholesterol, HDL and blood pressure during the four years of treatment. However LDL cholesterol decreased after four years of treatment. It is important to note that fat percentage dropped after one year of therapy and stayed stable thereafter. Similarly lean body mass increased after first year of therapy but slightly decreased during second year and stayed stable thereafter. A significant increase in height was noted indicating complete normalization of height after four years of GH therapy. The data suggested beneficial effects of GH on height if administered several years before puberty. Nevertheless hand and foot length, as well as arm span did not completely normalize during the four years. No adverse findings were noticed in regards to insulin dependent Diabetes Mellitus. However a significant decrease in BMI was noticed during the GH treatment. The Dutch prospective trial revealed that long term administration of a standard dose of 1mg/m^2/d has beneficial effects on children with PWS.[4]

GH plays a major role in synthesis of IGF-I as witnessed by low IGF-I values due to GH deficiency in children with PWS. Approximately 98% of IGF-1 is bound to one of 6 binding proteins (IGF-BP). IGFBP-3, a major carrier protein in the circulation, accounts for 90% of

all IGF binding.[8]. Consequently short stature and abnormal body composition is also associated with low IGF-I values. [2,6,9] A retrospective study in France compared changes in serum IGF-I, IGF binding protein 3 (IGFBP-3), IGF-I to IGFBP-3 molar ratio, and growth velocity during the first 2 yr of GH therapy in 33 children with PWS and 591 with GH deficiency (GHD). The mean initial dose of GH administered was 0.9 and 1 mg/m2/d in the PWS and GHD groups, respectively. Serum IGF-I and IGFBP-3 were measured at 0, 6, 12, and 24 months of GH therapy.[8]

At baseline children with PWS had a higher birth length and BMI, and lower birth weight than the GHD children. Baseline mean IGF-I levels were low in both groups but increased with GH treatment. Data revealed a higher serum IGF-I and IGFBP-3 in the PWS group despite of significantly lower GH doses in PWS children at 6, 12, and 24 months. However the IGF-I to IGFBP-3 molar ratio was lower in the children with PWS as compared to GHD group. IGF-I increased to a greater extent in PWS than GHD after GH treatment. Data analysis suggests an association between higher growth velocity and sensitivity to GH in PWS children during the first 6 months of the treatment despite of the low dosage.[8]

It is essential to address the efficacy of a treatment if the results are significant enough to be generalized. As mentioned previously GH treatment through the life span has exhibited beneficial effects for children as well as adults. US Adult Prader-Willi Syndrome Study, conducted a12 month open label multicenter trial, with thirty eight PWS adults between the ages of 17 and 49 years.[6] The GH treatment was initiated with 6 months dose optimization and 6 months stable treatment periods. During the 6 month dose optimization period, the treatment was initiated at the dose of 0.2mg/d which was increased monthly in0.2 mg/d

increments with a maximum of 1mg/d, as tolerated. The mean does of 0.6mg/d was maintained at a constant level over the subsequent 6 months of the study. The data revealed an 8.39% increase in LBM in males and 6.66% in females. The data also showed percent fat decreased from ~43 to 40 after 12 months. Even though HbA1c did not vary significantly, fasting glucose increased from ~81-87mg/dl but remained in normal range in 27 patients. However the prevalence of metabolic syndrome increased to 31% after GH treatment.

The study also performed thyroid function tests that revealed significant changes in T_3 but no positive effect was noticed on TSH. After the GH treatment T_3 improved confirming the association of thyroid abnormalities with unique abnormal body composition of PWS patients. Treatment dosage may be an important factor in order to consider the efficacy of the treatment. Water retention and edema is often associated with GH treatment which may be controlled with dose adjustment and judicious initiation of GH. Even though formal assessment of diet and physical activity was not included in the study design qualitative data provided significant information on the physical strength, associated with activity and exercise, revealing positive effects on subjects engaged in planned physical activities. The data suggested that GH treatment has beneficial effects on percent fat and LBM and it normalizes IGF-1 without glucose impairment.[6]

The effectiveness of GH treatment in regards to decrease in percent fat has been confirmed in many studies. The investigation of the effects of GH on regional fats cannot be neglected. Patients with PWS exhibit unusual body composition that is often associated with subcutaneous abdominal fat. The Scandinavian multicenter placebo control, double blind trial explored the effects of one year GH treatment on different fat compositions and LBM in

forty six adults, ages 16-50 years, with PWS. For the initial 4 weeks phase of the study, patients were treated with 0.3 or 0.4 mg/d if their body weight was below or above 100 kg, respectively. Doses were increased to 0.6 or 0.8mg/d for the next 11 months. Patients and caretakers were advised to keep the usual diet consistent. As majority of the cohort resided in special group homes, extent of caloric intake and exercise were controlled. [2]

The data revealed significant decrease in subcutaneous and visceral fat. However the difference in decrease of regional fats is notable. When compared with placebo group, subjects in GH treatment group demonstrated a decrease in subcutaneous fats up to 70.9 ml while visceral fat to 22.9 ml with a total fat mass decrees of 4.20 kg. Subsequently with the decrease in fat mass, LBM improved up to 2.25 kg in GH treatment group. Some studies suggest a decreased amount of visceral fat in PWS patients as compared to simple obesity. Interestingly, a gender difference was also noted; where male subjects had more decrease in visceral fat than female subjects. [2]

Results also revealed an increase in IGF-I level and a decrease in LDL cholesterol while no changes were noticed in total cholesterol, HDL or TG in GH treated group. Both placebo and GH treated groups did not reveal any changes in fasting glucose or fasting insulin. In addition, no changes were noticed in BMI. Mild pretibial edema was noticed in both GH treated and placebo group however less edema was reported in GH treated group after one year as compared with baseline. The 12 month study confirmed the effectiveness of GH treatment by demonstrating a decrease in total and regional fat mass and improvement of LBM.[2]

A follow up study further investigated the effects of long term GH treatment for two years, in the subjects of the Scandinavian study where 39 adults from both the placebo and GH treated groups received treatment. The study confirmed the previous findings by demonstrating consistent effects with short and long term GH treatment.[7]

Though research suggests potential benefits of GH treatment for children and adults with PWS, the specificity of a treatment cannot be judged unless a placebo treatment is utilized. In most cases a placebo treatment appears unethical; especially among younger subjects who could benefit with the treatment during certain time periods in their lives.

Many other factors demand justification for the efficacy of the GH treatment. Length of treatment is a significant factor that questions the effectiveness. Short term studies as compared with the long term studies did not reveal any significant variations. Some studies revealed a plateau in the outcome after a certain time period. However result may be different for certain variables indicating the fact that each variable may have a certain physiologic and genetic component that can alter the metabolic effect of the treatment. It will not be incorrect to speculate that GH treatment may play a maintenance role on some variables after a certain time period.

From the perspective of diet and lifestyle modification it is important to control the confounders. Hyperphagia is one of the main characteristic of PWS in children. Even though study protocol may demand diet control or consistency during the treatment, food consumption if not measured may drastically affect the results. Similar is the case with

physical activity; a strict physical activity regimen can alter the findings significantly. GH therapy may have more beneficial effects if it is strictly combined with controlled diet.

The effect of medication may also play an important role in the final outcome of the GH treatment. Other drugs used by patients may promote or reduce the effects of GH treatment. Treatment dosage is another important factor that needs further research. As different studies have revealed different dosages for subjects based on body's weight and surface area; the highest safe dose may vary based on individual cases. Some studies demonstrated treatment of pretibial edema with dose adjustment in some patients while others did not experience any symptoms.[2]

At current there seems to be no significant increased risk for side effects of GH treatment in people with PWS. However it will be beneficial to assess if the benefits from the treatment outweigh the side effects. Conversely, it should not be neglected that PWS is a relatively young disease with not enough data to base conclusions on. Studies are just beginning on the use of GH in infants and adults with PWS. Further studies are needed to outline risks and benefits of therapy in children and adults suffering from PWS.

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References:

1. Aaron L. Carrel, Susan E. Myers, Barbara Y. Whitman, Jens Eickhoff and David B. Allen, Long-Term Growth Hormone Therapy Changes the Natural History of Body Composition and Motor Function in Children with Prader-Willi Syndrome. *The Journal of Clinical Endocrinology & Metabolism*2010; Vol. 95, No. 3 1131-1136

2. Sode-Carlsen R, Farholt S, Rabben KF, Bollerslev J, Schreiner T, Jurik AG, Christiansen JS, Höybye C, One year of growth hormone treatment in adults with Prader-Willi syndrome improves body composition: results from a randomized, placebo-controlled study; *J Clin Endocrinol Metab*. 2010 Nov; 95(11):4943-50. Epub 2010 Aug 11.

3. Prader-Willi syndrome Genetic Home reference, Reviewed: October 2011, Published: December 2, 2012. National Institute of Health, - retreived Nov 23rd from http://ghr.nlm.nih.gov/condition/prader-willi-syndrome

4. De Lind van Wijngaarden RF, Siemensma EP, Festen DA, Otten BJ, van Mil EG, Rotteveel J, Odink RJ, Bindels-de Heus GC, van Leeuwen M, Haring DA, Bocca G, Houdijk EC, Hoorweg-Nijman JJ, Vreuls RC, Jira PE, van Trotsenburg AS, Bakker B, Schroor EJ, Pilon JW, Wit JM, Drop SL, Hokken-Koelega AC, Efficacy and safety of long-term continuous growth hormone treatment in children with Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2009 Nov;94(11):4205-15. Epub 2009 Oct 16.

5. Nelms Marcia, Sucher Kathryn, Lacey Karen, Roth, Sara Long, Nutrition Therapy and Pathphysiology.(2nd Edition, p 473t,480t) 2011 Wadsworth, Cengage Learning

6. Mogul HR, Lee PD, Whitman BY, Zipf WB, Frey M, Myers S, Cahan M, Pinyerd B, Southren AL.Growth hormone treatment of adults with Prader-Willi syndrome and growth hormonedeficiency improves lean body mass, fractional body fat, and serum triiodothyronine without glucose impairment: results from the United States multicenter trial. *J Clin Endocrinol Metab*. 2008 Apr;93(4):1238-45. Epub 2008 Jan 22.

7. Sode-Carlsen R, Farholt S, Rabben KF, Bollerslev J, Schreiner T, Jurik AG, Frystyk J, Christiansen JS, Höybye C.Growth hormone treatment for two years is safe and effective in adults with Prader-Willi syndrome. *Growth Horm IGF Res.* 2011 Aug; 21(4):185-90. Epub 2011 Jun 12.

8. Feigerlová E, Diene G, Oliver I, Gennero I, Salles JP, Arnaud C, Tauber M. Elevated insulin-like growth factor-I values in children with Prader-Willi syndrome compared withgrowth hormone (GH) deficiency children over two years of GH treatment. J Clin Endocrinol Metab. 2010 Oct;95(10):4600-8.

9. Burman P, Ritzén EM, Lindgren AC 2001 Endocrine dysfunction in Prader-Willi syndrome: a review with special reference to GH. Endocr Rev 22:787–799Bekx MT, Carrel AL, Shriver TC, Li Z, Allen DB 2003 Decreased energy expenditure is caused by abnormal body composition in infants with Prader-Willi syndrome. J Pediatr 143:372–376.