RESEARCH ARTICLE

EFFECTS OF GROWTH HORMONE ON MUSCLE STRENGTH, TONE AND MOBILITY OF CHILDREN WITH PRADER-WILLI SYNDROME

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Abstract

Objective

Prader-Willi Syndrome (PWS) is a genetic syndrome presenting with severe hypotonia and decreased agility. Growth Hormone (GH), which is often used in these patients to treat short stature and obesity, seems improve hypotonia, physical strength, activity, and locomotor developmental ability. The aim of this study was to find the effects of growth hormone on agility and strength of these patients.

Material & Methods

In a prospective randomized controlled clinical trial in an out-patient pediatric endocrine clinic in Tehran, 21 PWS children (12 boys and 9 girls, 4 to 9 years old) were divided into either GH-treated or control groups and followed for two years. Agility run, sit ups, weight lifting, and inspiratory and expiratory strength were considered as the main outcome measures.

Results

All the outcome measures of the GH treated group showed a significant improvement compared to the control group.

Conclusion

GH causes a significant improvement in agility and strength of PWS children.

Keywords: Preder-willi syndrome; PWS; growth hormone;agility; strength.

Introduction

Prader-Willi Syndrome (PWS), initially described in 1956, is now known to be caused by a deletion of the paternal allele in position 15q11–13 (~70% of patients) or a uniparental (maternal) disomy, affecting the same region or the whole chromosome 15 (1). Thus, PWS is a manifestation of genomic imprinting; the critical region of chromosome 15 is active only in the paternally inherited chromosome. Affected children are characterized by distinct facies, obesity, hypotonia, short stature, hypogonadism, and behavioral abnormalities (2). With an incidence of 1 in every 12,000 births, PWS is the most common syndromal cause of marked obesity.

Many features of PWS suggest hypothalamic dysfunction, some with endocrine implications including hyperphagia, sleep disorders, deficient growth hormone (GH) secretion, and hypogonadism (3–5). Growth of children with PWS is characterized by moderate intrauterine (average –1standard deviation score [SDS]) and postnatal growth delay. Usually, after the age of 2 or 3, when caloric intake increases and obesity begins to develop, growth rates become normal.However, catch-up in length/height relationship is less common. The hands and feet of these children

tend to be particularly small. Childhood growth rates are close to normal, but lack of normal pubertal growth often results in reduced adult stature (mean 146 cm for adult PWS female, 152 cm for adult PWS male). The slow growth and delayed skeletal maturation observed in some, but not all, PWS children contrasts with healthy obese children, in whom growth acceleration and bone age advancement are commonly seen with overnutrition. Growth impairment in PWS cannot be attributed to any known intrinsic bone or cartilage abnormality. Consequently, attention has focused on possible defective hypothalamic regulation of the growth process. Growth hormone responses to insulin, arginine, clonidine, L-dopa, or GH releasing hormone (GHRH) are reported to be low normal or blunted in PWS, as are sleep-induced GH secretion and 24-h integrated GH concentrations (3-6). Studies on consecutive patients with PWS have revealed GH levels <10 ng/mL following clonidine provocation in all patients (6-9).

Hypotonia is prenatal in onset, and is usually manifested as decreased fetal movement, abnormal fetal position at delivery, and increased need for assisted delivery or cesarean section. In infancy, there is decreased movement and lethargy with decreased spontaneous arousal, weak cry, and poor reflexes, including a poor suck that leads to early feeding difficulties and poor weight gain. Deep tendon reflexes are often spared. Assisted feeding through a feeding tube and/or special nipples with increased feeding times are invariably necessary. The hypotonia is central in origin. Mild-to-moderate hypotonia persists throughout life. Hypotonia is so characteristic that all newborns with unexplained persistent hypotonia should be tested for PWS (9, 10).

Gross motor and language milestones are delayed. Early milestones are reached on average at double the normal age (eg, sitting at 12 months, walking at 24 months, and words at 2 years). Cognitive disability is evident by school age. Most people with PWS are mildly mentally retarded (mean IQ: 60–70s), with approximately 40% having borderline mental retardation or low-normal intelligence and approximately 20% having moderate retardation. Regardless of measured IQ, most people with PWS have multiple severe learning disabilities and poor academic performance for their mental abilities. Articulation is poor. Most adults require sheltered residential and employment settings because of a combination of cognitive, behavioral and food-seeking characteristics (9, 10).

Most studies reported structural and functional muscle abnormalities in PWS: morphological abnormalities of contractile elements and mitochondria, type-2 muscle fiber atrophy, with type-2B fiber deficiency and increased immature type-2C muscle fibers decreased type-1 muscle fiber size, decreased CoQ10 levels in muscle tissue indicating abnormal mitochondrial function, and decreased strength of thoracic muscles and knee flexor and Only one study reported hypo-excitability of the cortical motor areas. Based on these preliminary results, it can be hypothesized that the clinical symptoms originate at least partly from innate cortical and/or muscle pathology and partly from a secondary phenomenon of disuse. Therefore, more research is necessary to study the relationship between clinical symptoms, hypotonia and decreased muscle mass and strength, and the presence of structural and functional abnormalities in muscles and motor cortex (11, 12).

Substantial information is accumulating to support beneficial effects of 12–36 months of GH therapy on improving body composition and linear growth in children with Prader-Willi Syndrome (PWS). However, perhaps of greatest importance to patients and their families is the hope that GH therapy would improve the child's physical strength, activity, and developmental ability. Early reports include anecdotal reports of dramatic gains in physical activity abilities, and many parents of our subjects also claimed striking improvements in physical stamina, strength, and agility. Specifically, they included new gross motor skills (e.g., independently climbing up the bus steps, carrying a medium-sized bag, and participating in a normal gym class without restrictions).

Materials & Methods

Twenty-two PWS children (12 boys and 10 girls, age range: 4 to 9 years) were selected among PWS patients who referred to a tertiary out-patient pediatric endocrine clinic in Tehran, and divided into two groups: 11 children (6 boys and 5 girls) received subcutaneous growth hormone [PEN NORDILET; Novonordisk 5 IU/ 1.5 ml] (1 mg/ per one square meter of body surface area)

every night for two years, while11 children (7 boys and 4 girls) in the control group did not receive any medication throughout the study.

The thyroid function test, standard growth hormone stimulation test with clonidine, and bone age determination with Greulich and Pyle method were done in all patients before starting the study. All cases were genetically proven to be PWS either either FISH or by LINKAGE studies. All the measures were obtained and recorded by 2 pediatric endocrinologists and one physiotherapist throughout the study.

All patients in the controlled group were examined by a pediatric neurologist and an otolaryngologist for possible risk of sleep apnea following the administration of growth hormone. We evaluated the patients every 3 months for their growth indexes, possible adverse effects of GH, and also the specific outcome measures of the study.

We used the objective measures of changes in physical function during GH treatment, including a timed run (second), broad jumps (cm), sit-ups (in 20 seconds), and weight lifting (kg by reps) (5-9). We also measured respiratory muscle forces including inspiratory and expiratory strengths (cm/H2O) using a spirometeric device.

Two patients dropped out (a girl in the growth hormone group due to disagreement of the parents, and a boy in the control group due to the emigration of the family), both in the first months of study.

We informed all the parents regarding possible hazards of therapy and obtained the written consent of the parents before starting the study. The study was conducted with the approval of the ethics committee of Pediatric Surgery Research Center of Mofid Children's Hospital and under the guidelines of the Declaration of Helsinki.

Results

There was no significant difference between the possible confabulating factors including age, height standard deviation score (HeightSDS), height standard deviation score of Prader-Willi patients ($HeightSDS_{PWS}$), body mass index (BMI), body mass index of Prader-Willi patients, and insulin like growth factor 1- standard deviation score (IGF-I SDS) between the case and control groups at the beginning of the study ($p< 0.001$) (Table 1).

Missing data analysis showed no significant difference in results after omitting the drop-out cases from the study.

Improvements in the speed of running, broad jump, sit-ups and arm curls after 12 months of GH treatment compared to controls were documented. Following 24 months of GH treatment, improvements in broad jumping and sit-ups were maintained, while further improvement was noted in running speed and arm curls (Table 2). Measurement of respiratory muscle forces was reliably obtained in these individuals. Increases in both respiratory muscle forces were seen after one year of therapy and maintained at 24 months (Table 2). Additionally, strength and agility data at 24 months significantly increased compared to 12-month data, as well as significant improvement compared to prior to GH therapy (Fig. 1).

Discussion

Our study showed a significant improvement in running speed, broad jump, sit ups and arm curls after 12 months of GH administration which was similar to Angulo, Myers and Carel studies (3, 5-9). On the other hand, we followed the patients for 24 months (12 months more). We found the broad jumping improved slightly but still significantly ($p<0.05$), although sit ups showed an insignificant increase between 12 and 24 months ($p=0.02$).

Motor problems in Prader-Willi Syndrome (PWS) are presumably related to abnormal body composition and certain neuromuscular abnormalities. Increased fat mass and decreased lean body mass are characteristics of PWS. As a result, muscle mass is decreased by 25-37%, which might explain partly the weakness and hypotonia. However, there are also structural and functional muscle abnormalities, and cortical motor areas are hypo-excitable in PWS patients. Moreover, disuse, as a result of decreased activity in PWS, could also contribute. GH treatment positively influences body composition, but does not normalize it. Training could prevent disuse and improves body composition. Therefore, GH treatment and training will probably enhance each other (12).

Although there are studies showing that growth hormone therapy causes an increased basal metabolic rate and oxygen consumption, and hence increases ventilatory

load which may elevate the risk of sleep apnea in these patients(13), our study showed significant increases in both respiratory (inspiratory and expiratory) muscle forces throughout the study, which was similar to the results of Myers et al. (7). Recently, Carrel et al. found that in contrast to significant improvements observed during the initial 24 months of GH therapy (5, 6), strength, and agility, neither improved nor regressed during an additional 24 months of GH therapy at any dose (6).

In spite of these gains in physical function, PWS children still remain less compared to non-PWS children for all studied parameters. While lack of a blinded, placebo-controlled study design admittedly weakens scientific validity of these findings, they do suggest that measured improvements in strength and agility are associated with "real-life" functional benefits to the children and their families.

However, the insight in the origin of severe motor problems and hypotonia, decreased muscle mass and strength in PWS children were not discussed in this study. On the other hand, it seems that the research on body composition and the effect of GH has brought a lot of benefits to patients with PWS in managing the imbalance between fat mass and LBM, which has a positive effect on motor performance and fitness in general.

Table 1: Strength and Agitiy Testing in PWS

	Treated Group n = 11			*Non-treated Group n = 9*	
	Baseline	*12 mo*	*24 mo*	*Baseline*	*12 mo*
Agility Run (s)	11.1 ± 6.1	9.4 ± 4.4[a,c]	8.9 ± 3.8[b]	10.3 ± 1.8	10.6 ± 0.4
Broad Jump (cm)	50.0 ± 28.1	60.1 ± 28.3[a,c]	69.3 ± 25.2[a]	44.8 ± 9.1	40.4 ± 8.3
Sit-ups (in 20 s)	9.1 ± 4.8	11.5 ± 4.7[a,c]	12.1 ± 4.8[a]	9.1 ± 3.4	9.3 ± 3.1
Weight Lifting (KG x reps)	30 ± 12	40 ± 33[a,c]	46 ± 25	29 ± 12	30 ± 13
Inspiratory strength (cm/H_2O)	45.8 ± 23	55.7 ± 18.7[c]	60.1 ± 28.3	44.8 ± 13.2	40.4 ± 13.9
Expiratory strength (cm/H_2O)	54.6 ± 23.9	69.4 ± 24.8[c]	62 ± 26.4	58.8 ± 22.1	46 ± 13.3

[a] <0.01 compared to baseline.
[b] <0.01 compared to baseline and 12 mo.
[c] <0.01 compared to 12 mo control values.

Table 2. Baseline Characteristics

	Growth hormone group	Control group
n (males/females)	10 (6/4)	10 (6/4)
Age (year)	7.2 ± 3.2	6.9 ± 2.3
HeightSDS	–3.22 ± 1.6[1]	–3.19 ± 1.4
$HeightSDS_{PWS}$	–0.11 ± 0.6[1]	–0.10 ± 0.8
BMISDS	0.89 ± 1.5[1]	0.81 ± 1.8
$BMISDS_{PWS}$	–0.33 ± 0.7[1]	–0.33 ± 0.6
IGF-I SDS	–2.11 ± 1.4[1]	–2.05 ± 1.5

Measures at baseline for the growth hormone and control groups. Data are expressed as "mean ± SD", standard deviation score (SDS) according to age- and sex-matched PWS reference values (14).
[1] $P \leq 0.001$; There was no significant difference between case and control groups at the beginning.

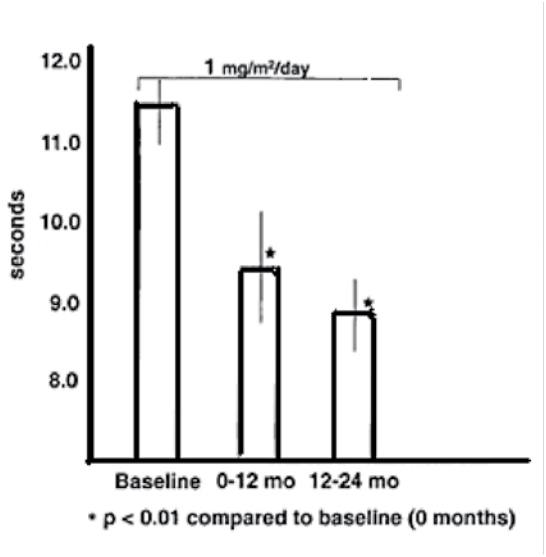

Fig1. GH therapy in PWS patients: Agility Run

References

1. Carrel AL, Huber S, Voelkerding KV. Assessment of SNRPN expression as a molecular tool in the diagnosis of Prader-Willi syndrome. Mol Diagn 1999;4(1):5–10.
2. Prader A, Labhart A, Willi H. Ein syndrom von adipositas, kleinwuchs, kryptorchismus and oligophrenie. Schweiz Med Wochenschr 1956;86:1260–1261.
3. Angulo M, Castro-Magana M, Uy J. Pituitary evaluation and growth hormone treatment in Prader-Willi syndrome. J Pediatr Endocrinol 1991;167–173.
4. Costeff H, Holm VA, Ruvalcaba R, Shaver J. Growth Hormone Secretion in Prader-Willi Syndrome. Acta Paediatr Scand 1990;79:1059–1062.
5. Carrel Al, Myers SE, Whitman BY, Allen DB. Benefits of long- term GH therapy in Prader- Willi syndrome: A 4-year study. J Clin Endocrinol Metab 2002;87:1581-1585.
6. Carrel AL, Myers SE, Whitman BY, Eickhoff J, Allen DB. Long-term growth hormone therapy changes the natural history of body composition and motor function in children with prader-willi syndrome. J Clin Endocrinol Metab 2010;95:1131-1136.
7. Myers SE, Whitman BY, Carrel AL, Moerchen V, Bekx MT, Allen DB. Two years of growth hormone therapy in young children with Prader-Willi syndrome: physical and neurodevelopmental benefits. Am J Med Genet A 2007;143:443-448.
8. Carrel AL, Myers SE, Whitman BY, Allen DB. Benefits of long-term GH therapy in Prader-Willi syndrome: a 4-year study. J Clin Endocrinol Metab 2002;87:1581-1585.
9. Carrel AL, Myers SE, Whitman BY, Allen DB. Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome: A controlled study. J Pediatr 1999;134:215–221.
10. Cassidy SB, Driscoll DJ. Prader-Willi syndrome. Eur J Hum Genet 2009;17:3-13.
11. Gunay-Aygun M, Schwartz S, O'Riordan MA, Cassidy SB. The changing purpose of Prader-Willi syndrome clinical diagnostic criteria and proposed revised criteria. Pediatrics 2001;108-110.
12. Reus L, Zwarts M, van Vlimmeren LA, Willemsen MA, Otten BJ, Nijhuis-van der Sanden MW. Motor problems in Prader-Willi syndrome: a systematic review on body composition and neuromuscular functioning. Neurosci Biobehav Rev 2011;35:956-69.
13. Wilson SS, Cotterill AM, Harris MA. Growth hormone and respiratory compromise in Prader-Willi Syndrome. Arch Dis Child 2006;91:349-50.