Curr Pediatr Res 2021; 25 (11): 1051-1055 *ISSN 0971-9032*
www.currentpediatrics.com

Effect of growth hormone therapy on Iraqi children with growth hormone deficiency.

Munib Ahmed Al-Zubaidi[1*], Sajjad H Kadhim Al-Shuwailli[2], Khalid Q Abd[2]

[1]Department of Pediatrics, College of Medicine, Baghdad University, Baghdad, Iraq

[2]Department of Pediatric Endocrinologist, Thi-Qar Specialized Diabetes, Endocrine and Metabolism Center, Thi-Qar, Iraq

Abstract

Background: Growth hormone deficiency is a rare condition in which the body does not make enough growth hormone. Incidence of child-onset GHD is approximately 1:4,000 to 1:10,000 live births. GH is essential for normal growth, muscle and bone strength, and distribution of body fat. The aim of study is to study the effect of growth hormone treatment on growth velocity during the first two years of treatment in children with growth hormone deficiency.
Patients and Methods: A retrospective study conducted at pediatric endocrinology outpatient clinic in children welfare teaching hospital/medical city in Iraq from 1st of November 2017 to thirty of October 2019 because of short stature due to GHD. Included 248 patients with GHD on growth hormone replacement of the following data were collected from the file records of the patients included in the research; name of patients, weight, height, sex of patients, bone age, growth velocity and age at the time of onset of the complaint and starting treatment. After the initiation of GH treatment, all patients were observed for height and weight with each visit, GV and BA after one and two years of treatment.
Results: The most common age of presentation was >10 years for male and female patients; most of them were males. For male patients; after the first and second year of treatment, the mean height velocity showed good response to GH treatment. For female patients; the mean height velocity also increased during the first and second years of treatment.
Conclusion: GH therapy for short stature due to GHD is safe and effective for all pediatric age groups before bone closure.

Keywords: GH therapy, Short stature, GV, Height velocity, Treatment, Iraq.

Accepted on 23rd November, 2021

Introduction

Short stature is a term applied to a child whose height or length below 3rd centile or less than 2 standard deviation for that specific age and sex [1]. Approximately 5% of children referred for evaluation of short stature have an identifiable pathologic cause [2].

Growth Hormone (GH), also called somatotropin or human Growth Hormone (hGH), peptide hormone secreted by the anterior lobe of the pituitary gland. It stimulates the growth of essentially all tissues of the body, including bone. GH is synthesized and secreted by anterior pituitary cells called somatotrophs. GH is vital for normal physical growth in children; its levels rise progressively during childhood and peak during the growth spurt that occurs in puberty [3]. Growth hormone is primarily known to promote longitudinal growth in children and adolescents, but has also various important metabolic functions throughout adult life [4].

Growth Hormone Deficiency (GHD) is a rare condition in which the body does not make enough Growth Hormone (GH). Incidence of child-onset GHD is approximately 1:4,000 to 1:10,000 live births. In children, GH is essential for normal growth, muscle and bone strength, and distribution of body fat. It also helps control glucose (sugar) and lipid (fat) levels in the body. Without enough GH, a child is likely to grow slowly and be much shorter than other children of the same age and gender [5]. Growth hormone deficiency is the most common pituitary hormone deficiency in children and can be isolated or accompanied by deficiency of other pituitary hormones. Isolated Growth Hormone Deficiency (IGHD) is the most frequent endocrinological disorder in children with short stature [6].

Patients with growth hormone deficiency associated with generalized hypopituitarism (panhypopituitarism) will also have deficiency of one or more other pituitary hormones (e.g. Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), Adrenocorticotropic Hormone (ACTH), Thyroid-Stimulating Hormone (TSH), Antidiuretic Hormone (ADH). Hypopituitarism can be primary (a pituitary disorder) or secondary to interference with hypothalamic secretion of specific releasing hormones that control anterior pituitary hormone (GH, FSH, LH, ACTH, TSH) production [7].

Screening tests for GHD in children with growth failure with no identified cause include bone age X-ray and serum IGF-1 and IGFBP-3 levels. A delayed bone age is more common in children with GHD. An MRI picture of the brain showing a small or ectopic (misplaced) pituitary gland supports a

diagnosis of GHD. The gold standard for diagnosing GHD is failure to increase GH levels in a Growth Hormone Stimulation Test (GHST). A GHST is performed in children after an overnight fast by giving a medication or medications (such as insulin, clonidine, arginine, glucagon, L-Dopa, etc.) to cause release of growth hormone into the blood and drawing blood frequently. If the highest growth hormone level obtained following two separate stimuli is <10 ng/mL, this is diagnostic of GHD [8].

A physical exam and measurement of height, weight, arms and leg lengths are the first steps to diagnosis, in addition to thorough medical history. Laboratory studies in Growth Hormone Deficiency (GHD) include the following: Thyroxin and thyroid-stimulating hormone.

Serum electrolytes

A low bicarbonate level may indicate renal tubular acidosis, which can result in growth failure. Abnormal electrolytes may indicate renal failure. CBC count and sedimentation rate: These studies may be helpful if inflammatory bowel disease is suspected.

Celiac panel

A small subset of patients with celiac disease may present with minimal to no gastrointestinal (GI) symptoms with growth failure or decreased height velocity. Karyotype: Girls with otherwise unexplained short stature should have a karyotype study to rule out Turner syndrome. Patients diagnosed with growth hormone deficiency should undergo an MRI of the head to exclude a brain tumor (e.g., craniopharyngioma) [9]. The treatment for growth hormone deficiency is administration of recombinant human growth hormone by subcutaneous injection (under the skin) once a day.

The length of growth hormone treatment depends on how well the child's height responds to growth hormone injections and how puberty affects the growth. Usually, the child is on growth hormone injections until growth is complete, which is sometimes many years [10]. Usual Pediatric dose for GH deficiency is 0.024 to 0.034 mg/kg subcutaneously once a day.

Possible side effects of HGH use include

Nerve, muscle, or joint pain, swelling due to fluid in the body's tissues (edema), carpal tunnel syndrome, numbness and tingling of the skin, nausea , vomiting and high cholesterol levels. HGH can also increase the risk of diabetes and contribute to the growth of cancerous tumors [11]. The aim of study is to study the effect of growth hormone treatment on growth velocity during the 1st two years of treatment in children with growth hormone deficiency.

Patients and Methods

Study design, setting, and time: This was a retrospective study conducted at pediatric endocrinology outpatient clinic in children welfare teaching hospital/medical city in Iraq from 1st of November 2017 to thirty of October 2019 because of short stature due to GHD. Study population and sample size: The study included 248 patients with GHD on growth hormone replacement out of 304 patients records reviewed.

Fifty six cases were excluded from the study as they receive growth hormone treatment for other indications such as Turner syndrome, Noonan syndrome, Prader-willi syndrome, and small for gestational age who fails to catch up growth at age of four years or some of them did not complete two years of treatment. An official agreement was taken from the hospital ethical committee to review the medical records for research purposes as long as the patient anonymity and confidentiality of their medical records are maintained. Growth Hormone Deficiency (GHD) is a rare condition in which the body does not make enough Growth Hormone (GH). Incidence of child-onset GHD is approximately 1:4,000 to 1:10,000 live births. In children, GH is essential for normal growth, muscle and bone strength, and distribution of body fat [5].

Work up

The following data were collected from the file records of the patients included in the research; name of patients, weight , height , sex of patients , bone age, growth velocity and age at the time of onset of the complaint and starting treatment. The subjects were divided into three groups according to the age at presentation as 3-5 years, 5-10 years and 10-15 years. The body weight was measured at diagnosis and then serially using ground weight scale and their height were measured serially using wall mounted stadiometer using the CDC data [12].

The criteria used to define a good first and second growth response were : 1-HV>+0.5 SD on the population HV reference curves, 2-HV>+1 SD on the population HV reference curves; height velocity was converted to SDS using Belgian reference data by Roelants et al. [13]. First and second years gain in HV (cm/year), were calculated as the increment in height between start of treatment and a measurement made after one and two years of GH treatment. Subcutaneous injection of GH at a dose of 0.3 mg/kg per week, 7 days weekly were given.

Follow up

After the initiation of GH treatment, all patients were observed for height and weight with each visit, growth velocity and left-hand radiogram for the evaluation of BA after one and two years of treatment.

Statistical analysis

It was carried out using the statistical package for Social Science Software Package (SPSS) version 26. The data were expressed as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Chi square-test was used to assess the association between the variables. P values less than 0.05 was considered statistically significant.

Result

Total number of patients included in this study was 248; 160 (64.5%) of them were male; female to male ratio was (1:1.8). The most common age of presentation was >10 years (48.8%) for both male and female; 68.6% of them were male.

For male patients; twenty six patients (16.3%) presented at age less than 5 years, fifty one patients (31.9%) presented between 5 and 10 years, eighty three patients (51.9%) presented between 10 and 15 years. For male patients less than 5 years; after the first and second year of treatment, the mean height velocity showed good response to GH treatment, 8.48 cm *vs.* 8.48 , SD=2.9 *vs.* 2.5 respectively ; P=0.9).

For those 5 to 10 years of male patients; the mean height velocity also increased but statistically the difference not significant between first and second years of treatment (7.6 cm *vs.* 6.9 cm, SD=2 *vs.* 2.3 respectively, P=0.09).

For those 10 to 15 years of male patients; the mean height velocity also showed good response to treatment during first and second years (8 cm *vs.* 8.7 cm, SD=2.4 *vs.* 2.6 respectively, P=0.1) Table 1.

Age at onset (years)	No. of patients	%	Growth velocity in 1st year		Growth velocity in 2nd year		P value
			Mean	SD	Mean	SD	
3-5	26	16.3	8.48	2.97	8.48	2.52	0.9
5-10	51	31.9	7.60	2.04	6.93	2.30	0.09
10-15	83	51.9	8.11	2.38	8.69	2.59	0.1

Table 1. Distribution of male patients according to the age at onset and the mean of the growth velocity during the 1st and 2nd year of growth hormone treatment.

Female patients were 88; fourteen patients of them (15.9%) presented at age less than 5 years, thirty six patients (40.9%) presented between 5 and 10 years, thirty eight patients (43.2%) presented between 10 and 15 years. In female patients less than 5 years; after the first and second year of treatment, the mean height velocity showed good response to GH treatment 9.3 cm *vs.* 7 cm, SD=3.5 *vs.* 2.5 respectively, P=0.01.

For those female with 5 to 10 years old; the mean height velocity also increased and statistically the difference was significant between first and second years of treatment (7.7 cm *vs.* 6.6 cm, SD=2.3 *vs.* 2.2 respectively, P=0.02).

For those 10 to 15 years of female patients; the mean height velocity showed good response during the first year and second years of treatment and statistically the difference was significant (8 cm *vs.* 6.9 cm, SD=2.5 *vs.* 1.8 respectively, P=0.007) (Table 2).

Age at onset (years)	No. of patients	%	Growth velocity in 1st year		Growth velocity in 2nd year		P value
			Mean	SD	Mean	SD	
3-5	14	15.9	9.29	3.49	7.12	2.45	0.01
5-10	36	40.9	7.69	2.31	6.59	2.21	0.02
10-15	38	43.2	8.04	2.48	6.91	1.84	0.007

Table 2. Distribution of female patients according to the age at onset and the mean of the growth velocity during the 1st and 2nd year of growth hormone treatment.

Discussion

In this study, the most common age of patients was >10 years (48.8%) for both male and female; and the majority of them were male (68.6%).

This result agreed with studies conducted by Alzahrani et al. in Jeddah , when showed that the mean age of patients was more than 10 years and majority of them were male 55.6%; by Cheri et al. in Canada as reported that the mean age of patients was 10 years or more in 64.6% and majority of them were male (50.7%), and by Ana et al. in Spain as reported that the mean age at diagnosis was 10.5 years, 69% of the patients were male [14-16]. This may be due to that the families don't seek medical help early and wait until the child enters the puberty.

In this study there was a good response in height velocity to GH treatment after first and second year in both sex less than 5 years especially male group, and this result agreed with Ranke et al. study at GH start, the mean HV (8.2 cm/year SD 3.3), after 1 year of GH treatment, mean HV 13.3 cm/year, SD 3.1; Boersma et al. study reported that early treatment of GHD may lead to adequate catch-up growth; after first year of treatment mean height SDS -2.5, after second year of treatment mean height SD score -2 and Huet et al. study reported that change in height SDS was +3.11 ± 2 SD [17-19]. These results suggested that early detection and treatment of GHD is a cost-effective strategy and results in greater improvements in height and growth velocity compared to a delayed treatment in childhood.

Increases in HV during the 1st and 2nd years of GH treatment in both sex for those between 5-10 years of age in this study and this agreed with Zavras et al. study which showed a good response to GH therapy during the follow-up, with a statistically significant increase from −1.82 SDS to −0.59 SDS Helena et al. study, the average height gain after one and two years of GH treatment were 1.00 ± 0.32 SDS and 1.50 ± 0.43 SDS, respectively, and Kamp et al. study, showed mean height SDS increased significantly from -2.6 (0.5) to -1.3 (0.5) after two years [20-22]. All these above results stressing that the early diagnosis and treatment before the statural impairment became evident was essential.

Regarding the response of HV to treatment for those above 10 years of age (males and females), there were a good response after the first and second year of treatment and this result agreed with Beth et al. study, showed that GV was significantly increase from baseline to one year of treatment 3.63 ± 0.32 cm/y (23) and Ross et al. study, showed significantly changes in HV; ΔHSDS observed for year 1, ranging from 0.4–0.7 and year 2 ranging from 0.6–1.0. [23,24].

In this study, mean height velocity for those between 5-10 years of age after first treatment year (mean HV=7.6 for male and female) were higher than second treatment year (mean HV=6.9 for male and 6.6 for female). This results similar to Saartje et al. study 110 children with GHD (69 males, 41 females), the median ΔHt SDS after the first treatment year was 1.03, while the median ΔHt SDS during the second year was 0.43 [25]

But disagreed with Helena et al. study, 121 patients included (64% boys), the age group was (5–10.8) years. The average height gain after one and two years on GH treatment was 1.00 ± 0.32 SDS and 1.50 ± 0.43 SDS, respectively [21]. These results go with fact; that maximum response to GH therapy occur in the first year of treatment.

Conclusion

In conclusion, GH therapy for short stature due to GHD is safe and effective for all pediatric age groups before bone closure.

References

1. Collett-Solberg PF, Jorge AA, Boguszewski MC, et al. Growth hormone therapy in children; research and practice-A review. Growth Horm IGF Res 2019; 44: 20–32.
2. Nilsson O, Weise M, Landman EB, et al. Evidence that estrogen hastens epiphyseal fusion and cessation of longitudinal bone growth by irreversibly depleting the number of resting zone progenitor cells in female rabbits. Endocrinology 2014; 155: 2892.
3. https://www.britannica.com/science/growth-hormone
4. Bidlingmaier M, Strasburger CJ. Growth Hormone. Handb Exp Pharmacol 2010; 195: 187-200.
5. Cook DM, Kevin Yuen CJ, Beverly Biller MK, et al. American association of clinical endocrinologist's medical guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients-2009 update. Endocr Pract 2009; 15(2):1-29.
6. https://www.hormone.org/diseases-and-conditions/growth-hormone-deficiency
7. Rodari G, Profka E, Giacchetti F. et al. Influence of biochemical diagnosis of growth hormone deficiency on replacement therapy response and retesting results at adult height. Sci Rep 2021; 11: 14553.
8. Andrew Calabria. Growth hormone deficiency in children (pituitary dwarfism). Perelman School of Medicine at The University of Pennsylvania. 2020.
9. Vaneeta Bamba, Robert P Hoffman. Pediatric growth hormone deficiency. Medscape 2018.
10. American academy of pediatrics and pediatric endocrine society. Growth hormone deficiency: A guide for families. Pediatric endocrinology fact sheet 2018.
11. https://www.doximity.com/pub/daniel-toft-md
12. Kuczmarski RJ, Ogden C, Grummer-Strawn L, et al. CDC growth chart: United States. Advance Data Report from vital and health statistics of the Center for Disease Control and Prevention, National Center for Health Statistics. 2000; pp: 1-28.
13. Roelants M, Hauspie R, Hoppenbrouwers K. References for growth and pubertal development from birth to 21 years in Flanders, Belgium. Ann Hum Biol 2009; 36(6): 680–94.
14. Alzahrani AK, Algethami AK, Barnawi G, et al. Differences in response to recombinant GH therapy on height gain in patients with idiopathic short stature *vs.* patients with GHD 2020; 12(3): e7319.
15. Cheri Deal, Susan Kirsch, Jean-Pierre Chanoine, et al. GH treatment of Canadian children: results from the GeNeSIS phase IV prospective observational study 2018; 6(3): E372-E383.
16. Ana Belén AJ, Martínez-Aedo Ollero MJ, López-Siguero JP. Efficacy and safety of replacement treatment in isolated GH deficiency. An Pediatr (Barc). 2019; 90: 285-92.
17. Ranke MB, Lindberg A, Albertsson-Wikland K, et al. Increased response, but lower responsiveness, to Growth Hormone (GH) in very young children (aged 0-3 years) with idiopathic GHD: analysis of data from KIGS. J Clin Endocrinol Metab 2005; 90: 1966–71.
18. Boersma B, Rikken B, Wit JM. Catch-up growth in early treated patients with growth hormone deficiency. Dutch GH working group. Arch Dis Child 2005; 72: 427–31.
19. Huet F, Carel JC, Nivelon JL, et al. Long-term results of GH therapy in GH-deficient children treated before 1 year of age. Eur J Endocrinol 2003; 140: 29–34.
20. Zavras N, Meazza C, Pilotta A. et al. Five-year response to growth hormone in children with Noonan syndrome and GHD. Ital J Pediatr 2015; 41: 71.
21. Helena-Jamin L, Hans F, Staffan N, et al. A prediction model could foresee adequate height response in children eligible for growth hormone treatment 2021.
22. Kamp GA, Waelkens, de Muinck Keizer-Schrama SMPF, et al. High dose GH treatment induces acceleration of skeletal maturation and an earlier onset of puberty in children with

idiopathic short stature. Arch Dis Child 2002; 87(3): 215-220.

23. Beth SF, Thomas FI, Theodore S, et al. Effect of growth hormone therapy on height in children with idiopathic short stature: A meta-analysis. Arch Pediatr Adolesc Med 2002; 156(3): 230-240.
24. Ross J, Lee PA, Gut R, et al. Factors influencing the one- and two-year growth response in children treated with GH: Analysis from an observational study. Int J Pediatr Endocrinol 2010; 2010: 494656.
25. Saartje S, Raoul R, Jean De S. Is a two-year growth response to GH treatment a better predictor of poor adult height outcome than a first year growth response in prepubertal children with GHD? Front Endocrine 2021; 12: 678094.

***Correspondence to:**

Munib Ahmed Al-Zubaidi

Department of Pediatrics

College of Medicine

Baghdad University

Baghdad

Iraq

E-mail: alisaadoon755@gmail.com