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# Factors Influencing Growth Response After Treatment in Children with Growth Hormone Deficiency

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## ABSTRACT

**INTRODUCTION:** Regular monitoring of growth and weight in children is crucial for effective child health surveillance. Growth retardation is suspected when a child's height falls below -2 standard deviations (SD) for age and sex, or when there is an abnormal growth velocity. Whereas endocrine causes account for less than 10% of growth retardation cases, they are essential to identify, as they require specific treatment. Growth Hormone Deficiency (GHD) is one such endocrine cause, with a prevalence ranging from 1 in 4,000 to 1 in 10,000 in Europe and the U.S. Advancements in diagnostic methods have improved early detection, allowing more children to benefit from treatment. The objective of this study is to investigate the therapeutic aspects and outcomes for children followed for GHD to identify the factors influencing the results of GH treatment.

**METHODS:** A descriptive retrospective study was conducted on patients hospitalized or followed for GHD at the Endocrinology Department of Farhat Hached University Hospital in Sousse from January 2000 to December 2020. Data were collected using a form that included epidemiological data, familial and personal history, clinical data at first consultation, bone age assessment, initial biological assessment, and substitutive treatment details.

**RESULTS:** The study enrolled 102 children (63 boys and 39 girls), with a mean age of 12±3.83 years at diagnosis. The mean height at diagnosis was 128±17 cm. GH deficiency was classified as complete in 63.7% and partial in 36.3% of cases. Associated deficits were found in thyrotropic (14.7%), corticotropic (19.6%), and gonadotropic (18.6%) axes. The average weekly dose of recombinant human growth hormone (rh-GH) was 0.7±0.12 IU/kg, and the mean stature gain under treatment was 17.5±14.5 cm, with a final height of 148±14 cm on average. Notably, younger children at the start of treatment showed greater stature gains, and regular adherence to treatment significantly correlated with improved outcomes. Overall, definitive stature gain was primarily associated with the frequency of GH injections and treatment regularity. The multivariate study showed that definitive stature gain was only associated with the frequency of GH injection and the regularity of treatment.

**CONCLUSION:** The study concludes that GH treatment can significantly enhance growth in children with GHD, but various factors, including timing of initiation, adherence to therapy, and individual patient characteristics, can affect whether the final adult height aligns with parental expectations. Stature gain can also be improved by emphasizing early diagnosis, patient education, and treatment adherence.

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**Keywords:** Growth retardation, Growth Hormone Deficiency, Children, Recombinant Human Growth Hormone, Stature Gain

**Abbreviation**
GHD: Growth Hormone Deficiency
rh-GH: recombinant human growth hormone
SD: standard deviations

## INTRODUCTION

The systematic monitoring of growth and weight in children is a key element in the surveillance of child health. A thorough medical history, reconstruction of growth curves, clinical examination, and simple paraclinical tests often allow for a quick orientation toward diagnosis. Growth retardation is suspected when a child's height is below -2 standard deviations (SD) for age and sex, when height is more than 1.5 SD below the genetic target height, or when there is an abnormal growth velocity accompanied by a change in the growth corridor (a loss of 2 SD) (1). The etiologies of growth retardation are numerous. Although endocrine causes represent less than 10% of these etiologies, they remain important to identify and must be investigated as they require specific and effective treatment (2).

Growth Hormone Deficiency (GHD) is one of the endocrine etiologies of GR. Its exact prevalence is unknown in Tunisia, while in Europe and the United States, it is estimated to vary between 1 in 4,000 and 1 in 10,000 (3,4). The diagnosis of GHD is suggested based on comprehensive anamnesis and clinical data and is confirmed through dynamic testing of growth hormone (GH) levels.

Thanks to advancements in diagnostic and therapeutic methods, particularly with the synthesis of recombinant GH since 1979, diagnoses have been made earlier, allowing more children to benefit from this treatment (5). However, there remains significant variability in the response to GH therapy.

This study aims to investigate the therapeutic aspects and outcomes for children followed for GHD to identify the factors influencing the results of GH treatment.

## METHODS

A descriptive retrospective study was conducted on patients hospitalized or followed for GHD at the Endocrinology Department of Farhat Hached University Hospital in Sousse from January 2000 to December 2020.

### Inclusion Criteria

The study included boys and girls aged 18 years or younger who presented with growth retardation defined by a height ≤ -2 SD, a slowdown in growth velocity (≤ -2 SD over one year or ≤ -1.5 SD over two years), or a deviation of at least 1.5 SD from the parental target height.

The diagnosis of GHD was confirmed through hormonal stimulation tests, where the maximum GH values did not exceed 10 ng/ml.

### Exclusion Criteria

Patients were excluded if:

Volume 1 Issue 1 (July-Dec 2024) | **ISSN**: 3049-0715

- Their clinical or paraclinical data were insufficient.
- They had only one test with a peak exceeding 10 ng/ml.

**Data Collection**

Data were collected using a form that included:

- Epidemiological Data: Age, gender, origin.
- Family and Personal History: Family history of short stature, amenorrhea, infertility, and personal history of intrauterine GR, birth weight, and height.
- Clinical Data at First Consultation: Height, weight, pubertal stage.
- Bone Age Assessment: Via X-rays of the left hand and wrist.
- Initial Biological Assessment: Including complete blood count, liver function tests, glucose levels, renal function tests, and hormonal evaluations.
- Substitutive Treatment Details: Name of the product, dosage, injection frequency, duration, and side effects.

**Statistical Methods**

Data were analyzed using SPSS version 20. Descriptive analyses calculated frequencies for qualitative variables and means for quantitative variables. Group comparisons utilized Student's t-test and chi-square tests. Univariate analysis calculated Odds Ratios to identify risk factors, while multivariate analysis employed linear regression to determine independent factors associated with outcomes, with a significance threshold set at $p < 0.05$.

**Ethical considerations**

The anonymity of the patients was maintained throughout the research process. All participants gave informed consent to participate in the research. The study has been approved by the Ethics Committee of the Faculty of Medicine of Sousse. This work does not involve any conflicts of interest.

**RESULTS**

We enrolled 102 children, 63 boys, and 39 girls, with an M/F sex ratio of 1.61. The mean chronological age at first consultation was 12±3.83 years, with a mean age of 12.3±3.8 years for boys and 11.9±3.8 years for girls, with no significant difference (p=0.5).

The mean birth weight was 3.02±0.58 Kg, and the mean birth height was 48±4 cm. In 22.2% of cases, the boys were non-pubescent, as were 33.3% of the girls.

The mean height at diagnosis was 128±17 cm, with a harmonious stature delay in all cases. Dynamic tests concluded that GH deficiency was complete in 63.7% (n=65) and partial in 36.3% (n=37) of cases. The hormonal investigation concluded an associated thyrotropic deficit in 14.7% of cases, a corticotropic deficit in 19.6% of children, and a gonadotropic deficit in 18.6% of cases.

The mean bone age was 9.5±3.6 years for boys and 9.3±3.9 years for girls. The delay between bone age and chronological age was found in 81% (n=51) of boys and 77% (n=30) of girls, with no significant difference.

MRI of the hypothalamic-pituitary region was performed in 61.8% of the children. Tumors of the sellar region were found in 8 patients: craniopharyngiomas (5 patients), meningiomas (two patients), and gliomas (one patient). MRI showed also interruption of the pituitary stalk in 17.5% of cases, empty Sella and hypoplasia of the anterior pituitary in 3.17% each.

Volume 1 Issue 1 (July-Dec 2024) | **ISSN**: 3049-0715

The genetic study was carried out on a 9-year-old girl who was the index case in a family with a PROP1 mutation (recessive genetic mutation responsible for somatotropic, lactotropic, thyrotropic, gonadotropic and corticotropic deficiencies with pituitary hypoplasia).

The mean weekly dose was 0.7±0.12 IU/Kg/week. The rate of injection of GH varied from one child to another and from one period to another. No side effects were noted. The average duration of treatment was 3 years, with extremes ranging from 6 months to 10 years. The treatment was taken irregularly in 17.3% of cases, linked to the patient (38.5%) or the health insurance (61.5%).

The mean stature gain under treatment was 17.5±14.5 cm with a maximum of 57 cm. Stature gain at the end of treatment in DS was on average 1±0.9 with a maximum of 3 DS. Bone age gain at the end of treatment averaged 4.6±3 years. The mean final height was 148±14 cm, with extremes ranging from 96 cm to 176 cm.

Boys had a greater definitive stature gain than girls, with no statistically significant difference (p=0.76). No correlation was found between birth weight and stature gain under treatment with a correlation coefficient r = -0.013 and p = 0.93. There was a negative correlation between age at the start of treatment and final stature gain (r = -0.346), and this correlation was statistically significant (p=0.002). Thus, the youngest children at the start of treatment will have the greatest stature gain.

The children with the smallest height at the start of treatment had a greater final stature gain, this negative correlation (r= -0.44) was statistically significant ($p=10^{-3}$). We found no correlation between parental target height and growth rate in the first year (r=0.033; p=0.82). We found a negative correlation between bone age at the start of treatment and growth velocity at the first year of treatment (r = -0.29), and this correlation was statistically significant (p= 0.01). Thus, the lower the bone age, the greater the stature gain. Definitive stature gain was greater for children who had not started puberty, with no statistically significant difference (p=0.63).

Stature gain was greater in cases of somatotropic deficiency associated with other deficits of the hypothalamic-pituitary axis compared to an isolated deficit but with no significant difference (p=0.09). There was no significant difference in stature gain between idiopathic and lesional DGH (p=0.9). There was no significant correlation between the mean GH peak (under glucagon-propranolol test or insulin tolerance test) and the final stature gain, with respective p values of 0.16 (r= 0.17) and 0.78 (r=-0.03). Children who took their treatment regularly had a greater definitive stature gain than those who did not, with a significant difference ($p=10^{-3}$). No correlation was found between GH dose in the first year of treatment and definitive stature gain (r= -0.16) (p=0.21). Injection on a 5/7 day schedule was associated with greater stature gain than 6/7 and 7/7, with a significant difference (p=0.04). There was a strongly positive (r=0.64) and statistically significant ($p=10^{-3}$) correlation between total stature gain and the duration of GH treatment.

After linear logistic regression, including the variables of interest about definitive stature gain, we found that definitive stature gain was only associated with the frequency of GH injection and the regularity of treatment (see Table 1).

## DISCUSSION

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The prevalence of GHD varies between 1 in 30,000 and 1 in 3,500 (6). There is currently no registry for this condition in Maghreb countries. GHD is a rare cause of stature-ponderal delay, with its frequency reported to range from 8.5% to 27% of cases of growth retardation in children.

The treatment with GH plays a crucial role in preventing complications associated with GHD. It not only enhances the stature growth of children but also reduces the risks linked to this hormonal deficiency (7).

In recent years, the dosage of recombinant human growth hormone (rh-GH) has slightly increased, varying based on the etiology of GHD and from one country to another. Current consensus recommendations suggest a dosage between 0.025 and 0.035 mg/kg/day (or 0.7 U/kg/week) (8). The nocturnal predominance of endogenous GH secretion supports the rationale for evening injections. Studies indicate that daily injections are significantly more effective than administering three injections per week (9).

The only contraindication for GH treatment is the presence of an active tumor, which is considered a temporary contraindication (10). For children with growth GHD, studies have shown that maintaining IGF-1 levels within the normal range is crucial for optimizing treatment outcomes and minimizing potential side effects (11,12). In our series, we adapted doses according to weight and growth velocity, but we did not reassess IGF-1 levels.

In the absence of GH treatment, the stature deficit remained very severe, with spontaneous adult height in individuals with somatotropic insufficiency varying between -3 and -7 SD. GH treatment has led to significant improvements in growth and adult height for subjects with somatotropic deficiency. All studies consistently show that catch-up growth is most pronounced during the first year of treatment, followed by a progressive decline in height gain in subsequent years (9). This trend was also observed in our series. The decrease in growth rate does not appear to be solely due to patients reaching their natural height trajectory but may also indicate acquired resistance to the effects of GH. In the literature, stature gain varies between 1.1 and 3.1 DS, and was 1±0.9 DS in our series.

Various studies in the literature have shown that GH treatment does not always result in an adult height consistent with the parental target height reference. This suggests that while GH therapy can improve height, it may not always meet the expectations set by parental height targets (13).

In addition, research has demonstrated that factors such as the age at which treatment begins and the patient's initial height can significantly influence outcomes. A study found that patients who started GH treatment later in life often experienced less favorable growth outcomes compared to those who began treatment earlier. Specifically, the mean adult height SD score for those treated was reported to be between -1.6 and -0.7, indicating that while GH treatment can lead to improvements, it may still fall short of achieving the genetic potential predicted by parental heights (14).

Furthermore, a comprehensive analysis highlighted that adherence to treatment regimens and the actual dosage received also play critical roles in determining growth outcomes. Children who received higher doses and maintained consistent treatment schedules were more likely to achieve heights closer to their target ranges (9).

In summary, while GH treatment can significantly enhance growth in children with deficiencies, various factors—including timing of initiation, adherence to therapy, and

individual patient characteristics—can affect whether the final adult height aligns with parental expectations (9,15).

In our series, we noted a delay in the diagnosis of GHD and the factors retained to influence stature gain after multivariate analysis were the frequency of GH injection and the regularity of treatment.

In summary, this study highlighted the importance of systematic monitoring and early diagnosis of GHD in children. The findings reveal that GHD significantly impacts growth, with a notable prevalence of associated hormonal deficiencies. Despite the advancements in treatment with rh-GH, the variability in growth response highlights the need for individualized treatment plans.

The results indicate that younger children at the onset of treatment tend to achieve greater stature gains, emphasizing the critical window for intervention. In addition, adherence to treatment schedules and regular monitoring of IGF-1 levels are essential for optimizing outcomes. While GH therapy can lead to substantial improvements in height, it does not always align with parental target heights, suggesting that further research is needed to explore additional factors influencing growth responses.

Generally, this study contributes valuable data on the therapeutic aspects and outcomes of GHD treatment, advocating for continued efforts to enhance diagnosis, patient education, and treatment adherence. By tackling these aspects, healthcare providers can improve growth outcomes and quality of life for children affected by GHD.

**REFERENCES**

1. Bouhours-Nouet N, Donzeau A, Coutant R. Conduite pratique devant une anomalie de la croissance. J Pédiatrie Puériculture. 1 avr 2017;30(2):67‑97.

2. Édouard T, Tauber M. Retard de croissance. J Pédiatrie Puériculture. 1 déc 2012;25(6):331‑45.

3. August GP, Lippe BM, Blethen SL, Rosenfeld RG, Seelig SA, Johanson AJ, et al. Growth hormone treatment in the United States: demographic and diagnostic features of 2331 children. J Pediatr. juin 1990;116(6):899‑903.

4. Vimpani GV, Vimpani AF, Lidgard GP, Cameron EH, Farquhar JW. Prevalence of severe growth hormone deficiency. Br Med J. 13 août 1977;2(6084):427‑30.

5. Wit JM, Reiter EO, Ross JL, Saenger PH, Savage MO, Rogol AD, et al. Idiopathic short stature: management and growth hormone treatment. Growth Horm IGF Res Off J Growth Horm Res Soc Int IGF Res Soc. avr 2008;18(2):111‑35.

6. Thomas M, Massa G, Craen M, de Zegher F, Bourguignon JP, Heinrichs C, et al. Prevalence and demographic features of childhood growth hormone deficiency in Belgium during the period 1986-2001. Eur J Endocrinol. juill 2004;151(1):67‑72.

7. Lee YJ, Choi Y, Yoo HW, Lee YA, Shin CH, Choi HS, et al. Metabolic Impacts of Discontinuation and Resumption of Recombinant Human Growth Hormone Treatment during the Transition Period in Patients with Childhood-Onset Growth Hormone Deficiency. Endocrinol Metab. avr 2022;37(2):359‑68.

8. Zhu J, Yuan K, Rana S, Jakki SL, Bhat AS, Liang L, et al. Long-acting growth hormone in the treatment of growth hormone deficiency in children: a systematic literature review and network meta-analysis. Sci Rep. 5 avr 2024;14(1):8061.

9. Coutant R, Nicolino M, Cammas B, de Buyst V, Tauber M, Hamel JF. Yearly Height Gain Is Dependent on the Truly Received Dose of Growth Hormone and the Duration of Periods of Poor Adherence: Practical Lessons From the French Easypod™ Connect Multicenter Observational Study. Front Endocrinol [Internet]. 20 janv 2022 [cité 28 sept 2024];12. Disponible sur: https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2021.790169/full

10. Pediatric Growth Hormone Deficiency Guidelines: Guidelines Summary [Internet]. [cité 28 sept 2024]. Disponible sur: https://emedicine.medscape.com/article/923688-guidelines

11. Drugs.com [Internet]. [cité 28 sept 2024]. Somatropin Dosage Guide + Max Dose, Adjustments. Disponible sur: https://www.drugs.com/dosage/somatropin.html

12. Collett-Solberg PF, Jorge AAL, Boguszewski MCS, Miller BS, Choong CSY, Cohen P, et al. Growth hormone therapy in children; research and practice - A review. Growth Horm IGF Res Off J Growth Horm Res Soc Int IGF Res Soc. févr 2019;44:20‑32.

13. Thomas M, Beckers D, Brachet C, Dotremont H, Lebrethon MC, Lysy P, et al. Adult Height after Growth Hormone Treatment at Pubertal Onset in Short Adolescents Born Small for Gestational Age: Results from a Belgian Registry-Based Study. Int J Endocrinol. 2018;2018(1):6421243.

14. De Ridder MAJ, Stijnen T, Hokken-Koelega ACS. Prediction of Adult Height in Growth-Hormone-Treated Children with Growth Hormone Deficiency. J Clin Endocrinol Metab. 1 mars 2007;92(3):925‑31.

15. Van Bunderen CC, Glad C, Johannsson G, Olsson DS. Personalized approach to growth hormone replacement in adults. Arch Endocrinol Metab. 10 janv 2020;63:592‑600.

**Table 1: Multivariate study of factors influencing stature gain under GH treatment.**

| Parameters | Initial model | | Final model | |
|---|---|---|---|---|
| | **OR** | ***p*** | **OR** | ***p*** |
| **Age at the start of treatment** | -0,48 | 0,002 | - | - |
| **Target size - final size** | 0,55 | 0,002 | - | - |
| **Isolated deficit** | | 0,09 | - | - |

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|---|---|---|---|---|
| **GH peak under glucagon challenge** | 0,17 | 0,16 | 0,32 | 0,01 |
| **Regularity of GH treatment** | | $10^{-3}$ | - | - |
| **Duration of GH treatment** | 0,8 | $10^{-3}$ | 0,58 | $10^{-3}$ |
| **Injection rhythm** | | 0,04 | - | - |