Comparison between the growth response to growth hormone (GH) therapy in children with partial GH insensitivity or mild GH deficiency

Comparação entre a resposta de crescimento ao tratamento com hormônio de crescimento (GH) em crianças com insensibilidade parcial ao GH ou deficiência de GH leve

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ABSTRACT

Objectives: GH therapy is still controversial, except in severe GH deficiency (SGHD). The objective of this study was to compare the response to growth hormone (GH) therapy in children with partial GH insensitivity (PGHIS) and mild GH deficiency (MGHD) with those with SGHD. **Subjects and methods:** Fifteen PGHIS, 11 MGHD, and 19 SGHD subjects, followed up for more than one year in the Brazilian public care service, were evaluated regarding anthropometric and laboratory data at the beginning of treatment, after one year (1st year) on treatment, and at the last assessment (up to ten years in SGHD, up to four years in MGHD, and up to eight years in PGHIS). **Results:** Initial height standard deviation score (SDS) in SGHD was lower than in MGHD and PGHIS. Although the increase in 1st year height SDS in comparison to initial height SDS was not different among the groups, height-SDS after the first year of treatment remained lower in SGHD than in MGHD. There was no difference in height-SDS at the last assessment of the children among the three groups. GH therapy, in the entire period of observation, caused a trend towards lower increase in height SDS in PGHIS than SGHD but similar increases were observed in MGHD and SGHD. **Conclusion:** GH therapy increases height in PGHIS and produces similar height effects in MGHD and SGHD. Arq Bras Endocrinol Metab. 2014;58(1):23-9

Keywords

Idiopathic short stature; growth hormone therapy; growth hormone deficiency; partial GH insensitivity

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RESUMO

Objetivos: O tratamento com GH é ainda controverso, salvo na deficiência grave de GH (SGHD). O objetivo deste estudo foi comparar a resposta ao tratamento com GH em indivíduos com insensibilidade parcial ao GH (PGHIS) e na deficiência moderada do GH (MGHD) com SGHD. **Sujeitos e métodos:** Quinze pacientes com PGHIS, 11 com MGHD e 19 com SGHD, seguidos por mais de um ano no Sistema Único de Saúde, foram avaliados antropométrica e laboratorialmente, no início, com um ano de tratamento e na última avaliação (tempo máximo de dez anos na SGHD, quatro anos na MGHD e oito anos na PGHIS). **Resultados:** O escore de desvio-padrão (EDP) da estatura inicial foi menor nos indivíduos com SGHD do que naqueles com MGHD e PGHIS. Embora o aumento no EDP da estatura no primeiro ano em comparação com o inicial não fosse diferente entre os grupos, o EDP da altura no primeiro ano de tratamento permaneceu menor na SGHD que na MGHD. Não houve diferença no EDP da estatura na última avaliação entre os três grupos. O tratamento com GH, no período completo da observação, provocou uma tendência a menor aumento no EDP da estatura nos pacientes com PGHIS que naqueles com SGHD, entretanto aumentos semelhantes foram encontrados nos grupos MGHD e SGHD. **Conclusão:** O tratamento com GH aumentou a estatura nos indivíduos com PGHIS e produziu efeitos similares na estatura em MGHD e SGHD. Arq Bras Endocrinol Metab. 2014;58(1):23-9

Descritores

Baixa altura idiopática; tratamento com hormônio do crescimento; deficiência de hormônio do crescimento; insensibilidade parcial ao GH

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INTRODUCTION

Growth hormone (GH) has been used to treat children with GH deficiency (GHD) since 1958. Due to the poor supply, the use of GH extracted from cadaveric pituitaries was limited to severe GHD (SGHD). In order to ensure treatment for children who needed it mostly, a GH stimulation test peak less than 5 ng/mL was required to initiate GH therapy. In 1985, after the description of four cases of Creutzfeldt-Jakob disease, recombinant human GH (rhGH) replaced cadaveric GH in the treatment of GHD (1,2). The unlimited production of rhGH allowed the offer of the treatment to more children, and the GH peak cutoff value during the stimulation test was increased to 7 ng/mL, and finally to 10 ng/mL). The Food and Drug Administration (FDA) approved the use of rhGH for GHD children and adults, and subsequently to chronic renal failure, Turner syndrome, AIDS cachexia, Prader-Willi syndrome, children born small for gestational age (SGA), idiopathic short stature (ISS), short bowel syndrome, Noonan syndrome and SHOX Deletion (3-5).

A GH concentration of 10 ng/mL determined by radioimmunoassay is equivalent to 7 ng/mL in monoclonal assays (6,7). Children with height of two or more standard deviations (SDs) below the mean for chronological age and sex in the absence of an identified cause are classified as ISS (5,8). There is a group of short children who exhibit high response to pharmacological tests (GH peak ≥ 40 mU/L or 18 ng/mL), with low or normal insulin-like growth factor-I (IGF-I) levels, that are considered by some authors as having partial GH insensitivity (PGHIS), with a potential responsiveness to higher dose of rhGH (9-12). However, it is not a consensus, and it is rather arguable.

Since 2010, in Brazil, with the current laboratory methods of chemiluminescence and fluorometry, the GH peak level required by the Health System to provide GH treatment for GHD children is less than 5 ng/mL (13). This demand excludes from treatment children with GH peak between 5 and 10 ng/mL, which might have mild GH deficiency (MGHD), as well as those with possible PGHIS. However, some children possibly bearing MGHD or PGHIS were treated in the public health care system in northeastern Brazil, in the state of Sergipe, before this law was determined. The assessment of GH therapy response in both groups can be very helpful and provide better understanding of the underlying process. This prompted us to compare the response to GH therapy in patients with MGHD and PGHIS with that observed in a group of children with severe GH deficiency (SGHD), in a preliminary attempt to analyze the usefulness of such approach in a public scenario.

SUBJECTS AND METHODS

Subjects

In a retrospective study, medical records of 86 children were analyzed. The records came from the Endocrinology Division of the University Hospital of Federal University of Sergipe, Brazil, who had used rhGH (HORMOTROP® AQ, Dong – A Pharmaceutical Co. Ltd, South Korea). GH dose was 30 µg/kg/day in severe GH deficiency, and 50 µg/kg/day in other conditions. Inclusion criteria were patients with short stature and serum IGF-I concentration below the mean for chronological age and gender, who had received GH therapy for at least one year. All of them had undergone stimulation test (clonidine or insulin hypoglycemia) and GH were measured by chemiluminescence (GH ICMA Immulite, Diagnostic Products Corporation, Los Angeles, CA) or fluorometric assays (Auto Delfia, Wallac, Turku, Finland). Exclusion criteria were incomplete medical records (n = 12), Turner syndrome (n = 10), chronic renal failure (n = 1), concomitant use of GnRH analogue treatment for central precocious puberty (n = 2), chronic disease, corticosteroid treatment, dysmorphic syndromes (n = 3), SGA (n = 4), and GH peak between 10 and 18 ng/mL (n = 9). Therefore, 45 children were selected for the study.

Subjects were arbitrarily classified according to GH peak in: a) PGHIS: GH peak ≥ 18 ng/mL, n = 15, 10 boys; b) MGHD: GH peak ≥ 5 and < 10 ng/mL, n = 11, 7 boys; and c) SGHD: GH peak < 5 ng/mL, n = 19, 10 boys. Seven individuals from this latter group had multiple pituitary deficits.

The study was approved by the Ethical Committee of Federal University of Sergipe and written consent was obtained from the guardians of all participants before enrolling them in the study.

Assessed variables and study design

Data on chronological age (CA), height, weight, body mass index (BMI), growth velocity (GV), pubertal stage, IGF-I levels and bone age (BA) were collected

in 3 moments from the medical records: just before starting rhGH (initial) treatment, after 1 year on rhGH therapy (first year), and at the last medical record (present), after 3.15 (2.77) years on treatment, range 1 to 10 years in SGHD, 2.42 (1.12) years; range 1 to 4 years in MGHD, 2.01 (1.71) years; range 1 to 8 years in PGHIS. Data regarding rhGH doses, duration of treatment and parents' height were also obtained. Mid-parental height (MPH) was calculated by the mean difference of the father and mother height, corrected by 13 cm according to the gender of the child. IGF-I was measured by the immunoradiometric assay, with double extraction and assay sensitivity of 0.8 ng/mL (Diagnostic Systems Laboratories, Inc., Webster, TX). The intra- and interassay variabilities were 2.3 and 2.6%, respectively.

Statistical analysis

Height and BMI were converted to standard deviation scores (SDS) for chronological age using the British data as the reference (14). Mid-parental height (MPH) was calculated by the mean of the father and mother height, corrected by 13 cm according to the child gender. Serum IGF-I SDS was calculated according to the data provided by the manufacturer for chronological age and gender. Variations (Δ) in Height-SDS, Weight-SDS, BMI-SDS, IGF-I-SDS, and BA between initial and present evaluations were calculated for each group.

Data with normal distribution are presented as means (standard deviations). Data without normal distribution are presented as medians (interquartile ranges). One-way ANOVA with Bonferroni *post-hoc* test was used to compare variables among the three groups (SGHD, MGHD e PGHIS), and paired *t* test was used to compare the initial and present doses within each group. Fisher's test was used to analyze the distribution pattern of pubertal stages in the groups. MANCOVA and ANCOVA were used to analyze possible influence of confounder variables in initial height SDS, 1st year height SDS, and present height SDS, and in Δ Height SDS, respectively. Statistical analysis was performed in the software SPSS/PC 18.0 (SPSS Inc, Chicago II). Probability values ≤ 0.05 were considered statistically significant.

RESULTS

As expected the GH peak were different among the 3 groups (p = 0.02). GH peak in the SGHD group 2.0 (1.4) ng/mL, was lower than in MGHD 7.1 (1.4) ng/mL (p < 0.0001), and PGHIS group 24.5 (7.7) ng/mL (p < 0.0001).

There were no differences in age or MPH values among the groups (Table 1). There was no difference in the frequency of pubertal individuals between SGHD (6/16) and MGHD group (5/9), but between SGHD and PGHIS (11/15, p = 0.003). No difference was found in the frequency of pubertal individuals between MGHD and PGHIS.

Table 1 also shows the initial, first year, and present anthropometric parameters of SGHD, MGHD, and PGHIS groups. Initial height-SDS was lower in SGHD than in MGHD (p < 0.01) and PGHIS (p < 0.001) groups. No difference was found in initial height-SDS between MGHD and PGHIS. The increase in 1st year height SDS in comparison to initial height SDS was not different between the groups, SGHD 0.49 (0.57), MGHD 0.51 (0.62), and GHPIS 0.21 (0.25). Height-SDS after the first year of treatment was still lower in SGHD than in MGHD (p = 0.03), but no difference was found at the last assessment (present) of the children. The significant difference between MPH SDS and initial height SDS between SGHD and PGHIS (p = 0.019) disappeared in the first year and at the last assessment.

Table 2 shows the initial, first year and present IGF-I levels, bone age, and GH doses of the three groups. Initial IGF-I SDS was lower in SGHD than in PGHIS (p = 0.001), but no difference was observed in initial IGF-I SDS between SGHD and MGHD or MGHD and PGHIS. First year and present IGF-I SDS were similar in the three groups. GH doses were similar, except in the first year when they were higher in PGHIS than in SGHG (p = 0.026) (Table 2).

Table 3 shows the variation in height-SDS, IGF-I SDS, and BA between the initial and present moments. GH therapy brought a lower increase in IGF-I SDS (p = 0.03), and a trend towards a lower increase in height SDS (p = 0.07) in PGHIS than in SGHD, while similar results were observed in MGHD and SGHD.

MANCOVA using initial height SDS, 1st year height SDS, and present height SDS as dependent variables, group as factor, and initial age, initial GH dose, duration of treatment and pubertal stage (defined as pubertal or non-pubertal) as cofactors, revealed that only duration of treatment had a significant effect (p = 0.001) of 0.469 (partial eta squared) with an observed power of 0.973. The model explained 51.7% (adjusted R squared) of the variability in these variables. ANCOVA using the Δ Height SDS as dependent variable, group

as factor, and initial age, initial GH dose and pubertal stage as cofactors, revealed that group and initial GH dose had significant effects ($p = 0.001$) of 0.339 and ($p = 0.027$) of 0.143 with observed power of 0.943 and 0.611, respectively. This model explained 47.1% of the variability in this variable (adjusted R squared).

Table 1. Initial, first year (1st), and present anthropometric parameters, and mid-parental height (MPH) of severe GH deficiency (SGHD), moderate GH deficiency (MGHD), and partial insensitivity to GH (PGHIS). Present assessment was done after 3.15 (2.77) years on treatment; range 1 to 10 years in SGHD, 2.42 (1.12); range 1 to 4 years in MGHD, 2.01 (1.71) years; range 1 to 8 years old in PGHIS. Data are expressed as means (standard deviations) except for the initial present height in SGHD and MGHD and first year height in MGHD, which are expressed as medians (interquartile ranges)

	SGHD	MGHD	PGHIS
Initial age (years)	10.8 (3.5)	10.7 (2.5)	11.9 (2.5)
Pubertal stage			
I (n)	10	4	4
II (n)	1	3	5
III (n)	3	2	5
IV (n)	2	-	1
Initial height SDS	-3.33 (1.37)	-2.14 (0.54)*	-2.15 (0.91)**
1st year height SDS	-2.92 (1.54)	-1.62 (0.83)*	-2.09 (1.03)
Present height SDS	-2.02 (1.20)	-1.28 (1.02)	-1.58 (1.01)
MPH SDS	-1.46 (1.06)	-1.27 (0.88)	-1.32 (0.62)
Initial height SDS – MPH SDS	-1.87 (1.37)	-0.94 (0.93)	-0.76 (0.80)*
1st year height SDS – MPH SDS	-1.39 (1.34)	-0.43 (1.05)	-0.57 (0.89)
Present height SDS – MPH SDS	- 0.56 (1.07)	-0.08 (1.11)	-0.19 (0.87)
Initial SDS BMI	-0.68 (1.33)	0.29 (1.01)	-1.16 (1.29)
1st year SDS BMI	-0.69 (2.22)	0.61 (1.60)	-1.16 (1.03)
Present BMI SDS	-0.16 (1.44)	0.21 (1.07)	-0.73 (1.27)
Initial growth velocity (cm/year)	3.51 (1,10)	3.47 (0.92)	4.27 (1.13)
1st year growth velocity (cm)	7.43 (3.59)	8.42 (4.50)	6.99 (2.62)
Present velocity (cm/year)	6.93 (3.06)	6.10 (2.31)	6.98 (2.92)

SDS: standard deviation score; * $p < 0.05$ and ** $p < 0.01$ compared with SGHD group.

Table 2. Initial, first year and present IGF-I levels, bone age (BA), difference between BA and chronological age (CA), treatment period and GH doses used in severe the GH deficiency (SGHD), moderate GH deficiency (MGHD), and partial insensitivity to GH (PGHIS) group. Data are expressed as means (standard deviations), except for present BA and initial dose in SGHD, which are expressed as medians (interquartile ranges). GH doses represent yearly intervals. GH doses represent yearly intervals. Present assessment was done after 3.15 (2.77) years on treatment, range 1 to 10 years in SGHD, 2.42 (1.12); range 1 to 4 years old in MGHD, 2.01(1.71) years; range 1 to 8 years in PGHIS

Variables	SGHD	MGHD	PGHIS
Initial IGF-I SDS	-2.12 (0.65)	-1.58 (0.71)	-1.11 (0.71)**
1st year IGF-I SDS	-1.16 (2.06)	-0.24 (1.51)	-0.51 (1.31)
Present IGF-I SDS	0.17 (1.41)	0.20 (1.31)	-0.22 (1.59)
Initial BA (years)	8.10 (3.32)	9.50 (3.10)	11.51 (2.34)*
1st year BA (years)	10.32 (2.35)	10.80 (2.28)	12.33 (2.88)
Present BA (years)	12.00 (4.13)	13.62 (1.76)	13.06 (1.93)
Initial CA-BA (years)	3.04 (2.70)	1.28 (1.31)	1.41 (2.0)
1st year CA-BA (years)	2.12 (1.81)	2.17 (1.66)	1.99 (2.05)
Present CA-BA (years)	3.5 (2.32)	1.62 (1.84)	2.14 (1.48)
Initial dose (µg/kg/day)	47.36 (13.90)	50.00 (12.29)	51.53 (7.40)
1st year dose (µg/kg/day)	45.55 (9.56)	50.30 (11.78)	57.33 (9.78)*
Present dose (µg/kg/day)	49.61 (12.90)	56.00 (16.08)	56.22 (9.82)
Treatment period (years)	3.1 (2.8)	2.4 (1.1)	2.0 (1.0)

SDS: standard deviation score; * $p < 0.05$ and ** $p < 0.01$ compared with SGHD group.

Table 3. Variation of Height-SDS (Δ Height-SDS), of BMI-SDS (Δ BMI-SDS), of IGF-I-SDS (Δ IGF-I-SDS), of Bone Age (Δ BA) in years, and of the difference between Chronological Age (CA) and Bone Age (Δ CA-BA) from the initial to the present assessment in severe GH deficiency (SGHD), moderate GH deficiency (MGHD) and partial insensitivity to GH-IGF-I (PGHIS). Data are expressed as means (standard deviations). Present assessment was done after 3.15 (2.77) years on treatment, range 1 to 10 years in SGHD, 2.42 (1.12) years; range 1 to 4 years in MGHD, 2.01(1.71) years; range 1 to 8 years in PGHIS

Variables	SGHD	MGHD	PGHIS
Δ Height SDS	1.30 (1.22)	0.81(0.85)	0.54 (0.50)
Δ BMI SDS	0.51 (0.99)	-0.01 (0.88)	0.41 (1.13)
Δ IGF-I SDS	2.42 (1.40)	2.25 (1.08)	1.04 (1.31)*
Δ BA (years)	4.91 (3.41)	3.71 (1.49)	1.50 (1.17)*
Δ CA-BA (years)	**1.04 (1.33)**	**0.48 (0.68)**	**0.95 (1.29)**

SDS: standard deviation score; * $p < 0.05$ compared with SGHD group.

DISCUSSION

The main finding of this study was that, despite the higher initial height SDS of MGHD and PGHIS children in comparison to SGHD, they presented substantial height gain with present height SDS close to MPH SDS, probably due to the increase in IGF-I SDS in the three groups. While MGHD and SGHD behave similarly in response to rhGH therapy, a lower increase in IGF-I SDS was found in PGHIS compared to SGHD. The lower increase in IGF-I levels could, at least in part, explain the trend towards the small increase in height SDS observed in PGHIS group compared to SGHD.

Besides the historical GH indication to SGHD, nowadays, GH is indicated for nine non-GH deficient conditions, including ISS (3,4,15,16). ISS is a condition where individuals have SDS height less than -2, without evidence of endocrine, systemic, nutritional, or chromosomal abnormalities. It can be considered as part of the ongoing process that is limited between GHD and normality, covering different degrees of GH secretion and responsiveness (17,18). Although, ISS definition might include GH peak greater than 10 ng/mL (8), in our study we selected a particular subgroup that we called PGHIS that did not include children with GH peak between 10 and 18 ng/mL. PGHIS is defined as a variant of the GH insensitivity syndrome (Laron syndrome), characterized by a smaller reduction in stature, without facial abnormalities and with IGF-I concentrations near the lower limit of normality. In theory, PGHIS can be overcome by an exogenous administration of GH (8,11,19,20). Therefore, in these patients, the classic IGF-I generation test is not useful (19).

Heterozygous mutations in the GH receptor or post-signaling defects may be the cause of stature reduction in PGHIS (21,22). As molecular screening is restricted to a few centers, our data suggest that the hormonal PGHIS diagnosis can be sufficient for the indication to treatment with GH. The data also show that short children with GH peak ≥ 18 ng/mL and IGF-I levels below the mean may benefit from rhGH treatment. Furthermore, GH therapy in children with PGHIS may have consequences beyond the height, considering that these children have more fat (18), probably due to impairment of lipolytic and anabolic actions of GH (23-26).

The response to GH therapy with titrated doses to keep IGF-I in normal range, was similar in SGHD and MGHD. The difference between MPH and present height reinforce this finding. Based on experience and considerable research since the 1980s, the SGHD group would be expected to have a higher height response to replacement doses of GH. Our data suggest a superposition of height response between children with GH peak less than 5 ng/mL and children with the GH peak between 5-10 ng/mL with the schedule of treatment used. Whereas the majority of children with GH deficiency should be located in this last group (27), it seems exaggerated the requirement of the cutoff value of 5 ng/mL for treatment. It is possible that GH secretion in the range 5-10 ng/mL is enough in children with normal height and perfect GH-IGF-I axis, but not in short children with abnormalities in this axis (8).

Our MGHD group increased their SDS height in the first year by 0.5, but this was not observed in the PGHIS group. The lower increase in height SDS in PGHIS may be consequent to the lower increase in IGF-I. Approximately one third of children with GH deficiency or ISS fail to increase the SDS height by 0.5 during the first year of treatment (8,28), suggesting that they require higher dose of GH to surpass any

possible partial GH or IGF-I insensitivity. This finding indicates that GH dose in PGHIS should be titrated to keep IGF-I SDS in the upper range of normality, ideally around +2, as suggested by Cohen and cols. (8). This author compared two groups of prepubertal children with subnormal IGF-I: GHD (peak GH less than 7 ng/mL) and ISS (peak GH greater than 7 ng/mL). In the ISS, the strategy to keep SDS IGF-I around +2 required higher doses of GH (median 65 and 119 mg/kg/day, respectively), suggesting partial PGHIS in the second group. An increase of 0.3 to 0.5 SDS in height has been considered a successful first year response to GH therapy in ISS children, although this response is highly variable and dose dependent (5). Our cutoff of 18 ng/mL surely selected individuals with higher probability of expressing some degree of PGHIS in this spectrum of patients. It is important to point out that this group may include some patients with partial IGF-I insensitivity. This does not invalidate our findings, since these patients would also benefit from the higher IGF-I levels provided by the GH therapy with a more intense saturation of the IGF-I receptors.

Safety profile was not assessed in this study, as it demands several years after GH discontinuation. Nevertheless, GH treatment seems to be safe and the concept of individualization of therapy increasingly expands (8,12,27,29-34). Despite the controversy of the French (35) arm, with 30% increased risk of death with GH doses higher than 50 µcg/kg/day, which was not observed in the Dutch, Belgian, and Swedish (36) arm of the "Santé Adulte GH Enfant (SAGhE)", FDA believes that the benefits of continuing GH therapy outweighs the potential risk (37).

Our study has some features driven from the real world in which was done. One such characteristic is the more advanced pubertal stage in the PGHIS group. As the increase in final height in ISS is mainly due to the prepubertal growth and it is correlated with the growth velocity in the first year of treatment (38,27), the larger proportion of pubertal children in PGHIS group may have reduced the time of growth induced by GH therapy in these children. Pubertal status can influence the GH treatment response by reducing the duration of treatment, the most relevant co-factor to the height effect, in our analysis. We must also consider that a degree of IGF insensitivity may be present in some patients from this group, making us wonder if higher IGF-I levels would be necessary to reach the same outcome observed in the MGHD and SGHD groups. But in real world, while SGHD children are easily diagnosed, the diagnosis of PGHIS is usually delayed as physicians wait for a possible catch-up that eventually does not occur. As the duration of GH treatment mostly influenced height gain, physicians may synchronize duration of treatment with tempo of growth.

A limitation of this study was not having included control groups of normal or ISS children without treatment. A comparison with normal children by expressing data as SDS for sex and chronological age was made in order to minimize this problem. Another possible criticism to our data could be a small number of subjects recruited, due to our strict exclusion criteria in patients of the public health service, reducing the statistical power to reveal subtle differences. Anyway, this paper reports the largest number of PIGHS individuals treated with GH published so far. A third limitation was the criterion of inclusion, using serum IGF-I concentration below the mean for chronological age and gender. We adapted it to short children with low height velocity, from the last international consensus in which, in a short patient with normal height velocity, plasma IGF-I level above the mean for age and gender would not require GH testing (5).

In conclusion, the results seem to indicate that PGHIS and MGHD can benefit from GH therapy. Maybe a higher GH replacement dose is necessary in PIGHIS to reach the same height gain, as a higher increase in IGF-I levels seems to be related with a better outcome. Further studies may assess the efficacy and safety of this of this approach.

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