

# Provocative Tests in the Diagnosis of Childhood Onset Growth Hormone Insufficiency



## O Papel dos Testes de Estimulação Farmacológica no Diagnóstico da Deficiência de Hormona do Crescimento em Crianças e Adolescentes

Jean-Pierre GONÇALVES<sup>1,4</sup>, Filipa CORREIA<sup>2</sup>, Helena CARDOSO<sup>3</sup>, Teresa BORGES<sup>3</sup>, Maria João OLIVEIRA<sup>3</sup>  
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### ABSTRACT

**Introduction:** The incidence of short stature associated with growth hormone deficiency has been estimated to be about 1:4000 to 1:10000. It is the main indication for treatment with recombinant growth hormone.

**Objectives:** The aims of the study were to evaluate the results of growth hormone stimulation tests and identify the growth hormone deficiency predictors.

**Material and Methods:** A cross-sectional, analytical and observational study was conducted. We studied all the children and adolescents submitted to growth hormone pharmacological stimulation tests between January 2008 and May 2012. Growth hormone deficiency diagnosis was confirmed by two negatives growth hormone stimulation tests (growth hormone peak < 7 ng/ml). The statistical analysis was performed using student t-test, chi-square, Pearson correlation and logistic regression. Statistical significance determined at the 5% level ( $p \leq 0.05$ ).

**Results:** Pharmacological stimulation tests were performed in 89 patients, with a median age of 10 [3-17] years. Clonidine ( $n = 85$ ) and insulin tolerance test ( $n = 4$ ) were the first growth hormone stimulation tests performed. Growth hormone deficiency was confirmed in 22 cases. In cases with two growth hormone stimulation tests, the growth hormone peak showed a moderate correlation ( $r = 0.593$ ,  $p = 0.01$ ). In logistic regression model height (z-score) and the growth hormone peak in first stimulation test were predictors of growth hormone deficiency diagnosis (each one unit increase in z-score decrease the growth hormone deficiency probability).

**Discussion:** Measurement of IGF-1 cannot be used in diagnosing growth hormone deficiency.

**Conclusion:** Auxological criteria associated with a positive test seems to be a reliable diagnostic tool for growth hormone deficiency.

**Keywords:** Growth Disorders; Human Growth Hormone/blood.

### RESUMO

**Introdução:** A incidência da deficiência de hormona do crescimento é de 1:4000 a 1:10000, sendo a principal indicação para tratamento com hormona do crescimento recombinante.

**Objectivos:** Avaliar os resultados dos testes de estimulação da hormona do crescimento e identificar factores preditivos para o diagnóstico da deficiência de hormona do crescimento.

**Material e Métodos:** Estudo observacional, analítico e transversal. Foram analisados dados clínicos e auxológicos e os resultados dos exames de diagnóstico de crianças e adolescentes submetidos a testes de estimulação farmacológica da hormona do crescimento (01/01/2008 a 31/05/2012). O diagnóstico definitivo de deficiência de hormona do crescimento foi efectuado mediante dois testes com estímulos farmacológicos diferentes negativos (pico máximo da hormona do crescimento < 7 ng/mL) ou um teste negativo associado à presença de alterações anatómicas da região hipotálamo-hipofisária, observadas na ressonância magnética cerebral. Para análise estatística, foram realizados o testes de t student, do qui-quadrado, correlação de Pearson e a regressão logística. Foi considerado como nível de significância estatística ( $p$ ) um valor igual ou menor que 0,05.

**Resultados:** Realizaram-se testes de estimulação em 89 doentes, com mediana de idade igual a 10 [3-17] anos, 67% do sexo masculino e 77% pré-púberes. Os fármacos utilizados no primeiro teste de estimulação foram a clonidina ( $n = 85$ ) e a insulina ( $n = 4$ ). Foram diagnosticados 22 casos de deficiência de hormona do crescimento. Nos casos submetidos a dois testes, os valores máximos de hormona do crescimento apresentaram uma correlação moderada entre si ( $r = 0,593$ ,  $p = 0,01$ ). Verificou-se que as variáveis estatura (z-score) e pico máximo de hormona do crescimento obtido no primeiro teste têm valor preditivo no diagnóstico de deficiência de hormona do crescimento.

**Discussão:** A determinação do IGF-1 não demonstrou ser preditor de deficiência de hormona do crescimento.

**Conclusão:** Os testes de estimulação são uma ferramenta de diagnóstico da deficiência de hormona do crescimento e que devem ser enquadrados nos parâmetros clínicos e auxológicos.

**Palavras-chave:** Alterações do Crescimento; Hormona do Crescimento Humano.

### INTRODUCTION

Growth hormone (GH), secreted by the anterior pituitary somatotrophic cells and released into systemic circulation, is responsible for post-natal longitudinal growth, lipid me-

tabolism regulation, bone apposition, skeletal and cardiac muscle mass growth and blood pressure control. It also stimulates insulin-like growth factor (IGF-1) liver production,

1. Serviço de Pediatria. Hospital de Braga. Braga. Portugal.

2. Serviço de Pediatria. Hospital do Alto Ave. Guimarães. Portugal.

3. Unidade de Endocrinologia Pediátrica. Centro Hospitalar do Porto. Porto. Portugal.

4. ICVS/3B's Laboratório Associado. Instituto de Investigação em Ciências de Saúde. Escola de Ciências da Saúde. Universidade do Minho. Braga. Portugal.

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which is released into the systemic circulation, acting locally in a paracrine fashion, in peripheral tissues such as bone, cartilage and muscle. Circulating IGF-1 is almost entirely bound to the insulin-like growth factor binding protein 3 (IGFBP-3)<sup>1,2</sup> and is GH-dependent.<sup>3</sup>

GH deficiency (GHD) may be found with an incidence of 1:4,000 to 1:10,000 and is a major indication for replacement recombinant GH therapy.<sup>4</sup> GHD may relate to brain, hypothalamic or pituitary abnormalities.

GHD may be classified as severe/moderate and complete/incomplete.<sup>5,6</sup> In the absence of a gold standard, diagnosis is based on clinical, auxological, analytical and radiological parameters.<sup>7</sup>

Despite their non-consensual predictive value, stimulation tests are still used in GHD diagnosis confirmation and for starting replacement recombinant GH therapy.<sup>7,8</sup> At least two different stimulation tests with peak GH levels below 7 ng/ml are required, in order to confirm GH insufficient secretion.<sup>9-11</sup> Our study aimed to assess the results of stimulation tests for GH secretion, more specifically the concordance of GH peak secretions between two different pharmacological stimuli and the identification of GHD predictive factors in the patients whose diagnosis is confirmed by stimulation tests.

## MATERIAL AND METHODS

This was an observational, cross-sectional and analytical study involving children and adolescents who underwent GH secretion pharmacological stimulation tests at the Paediatric Endocrinology Unit from Porto's Hospital Centre, between January 2008 and May 2012.

Data collection was based on a retrospective analysis of clinical records. The parameters related to patient height, body mass index (BMI), growth velocity (GV), target height (TH), GH peak of secretion (ng/ml), IGF-1, IGFBP-3, bone age (BA) and MRI (magnetic resonance imaging) of the brain (the latter if applicable). Patient height, BMI, GV and TH were standardized according to patient's age and gender and represented by z-scores. Height, TH and GV z-scores were determined and interpreted using Tanner-Whitehouse curves.<sup>12,13</sup> BMI z-score was assessed by Cole's curves.<sup>14</sup> IGF-1 and IGFBP-3 were dichotomically expressed using the 2.5<sup>th</sup> percentile as reference value for chronological age and gender (Immuline 2000; Diagnostic Products Corp., Los Angeles, CA).<sup>15</sup> Bone age was determined by the Greulich and Pyle method.<sup>16</sup>

According to the rules of the National Commission on Standardisation of Growth Hormone (*Comissão Nacional de Normalização da Hormona do Crescimento* [CNNHC]), a GH secretion peak < 7 ng/ml upon adequate pharmacological stimulation was considered indicative of GHD.<sup>11</sup> Pharmacological stimulation tests were classified as negative when GH secretion peak was < 7 ng/ml and positive when  $\geq$  7 ng/ml. Confirmation of GHD required two different negative pharmacological stimulation tests.

Two study groups were defined: group 1 (patients with two negative tests) and group 2 (patients with one negative and one positive test)

Results were described through dispersion measures (mean  $\pm$  SD). Variables by groups (1 and 2) were compared by t-student and chi-square tests, applied for quantitative and qualitative variables, respectively.

Pearson's correlation was used to determine correlation between GH secretion peaks observed in the first and second tests.

Logistic analysis was used for possible GHD predictors, confirmed by two negative tests. Two models were defined, one with the variable IGF-1 (model 1) and the other with height and peak GH-adjusted IGF-1 obtained in the first test (model 2).

Data were analysed using SPSS (version 19.0) software. The results with  $p < 0.05$  were considered as statistically significant.

## RESULTS

The distribution of our group of patients by pharmacological stimuli and number of performed tests is shown in Figure 1. Eight-nine patients underwent stimulation tests, with a median age of 10 [3-17] years old, 67% male and 77% in puberty stage 1.

Clonidine ( $n = 85$ ) and insulin ( $n = 4$ ) were used in the first stimulation test.

A first negative test was obtained in 29 patients. From these, 24 underwent a second test [clonidine ( $n = 2$ ), insulin-induced hypoglycemia ( $n = 5$ ) and L-dopa ( $n = 17$ )].

From the 24 patients who underwent a second test, 22 had a negative result, allowing for GHD confirmation.

Even upon a first negative test, five patients did not undergo a second test due to loss to follow-up ( $n = 1$ ), presence of the Silver Russell syndrome ( $n = 1$ ), Kallman syndrome ( $n = 1$ ) or hypothalamic-pituitary axis abnormality with brain MRI abnormalities ( $n = 2$ ).

From the 60 patients in whom GHD was excluded after the first test:

a) Thirty-three patients showed a height z-score < -2 SDS (10 patients with constitutional maturation and growth retardation criteria and 17 patients with familial short-stature criteria);

b) Twenty-seven patients showed a height z-score  $\geq$  -2 and one of the following criteria: height z-score < -1,5 related to TH, GR z-score < -2 for one year and < -1.5 for two years.

Bone age and IGF-1 levels were obtained in all patients, IGF BP3 levels in 35 patients and MRI of the brain in 32 patients.

Patients with GHD (group 1) showed lower average height (z-score) (-2.9  $\pm$  0.6 vs. -2.1  $\pm$  0.9,  $p = 0.001$ ) and lower GH maximum secretion peak in the first test (4.0  $\pm$  2.1 vs. 16.1  $\pm$  6.5,  $p = 0.001$ ), when compared to the remaining patients (group 2) (Table 1), with statistically significant values. The percentage of patients with lower IGF-1 and IGF BP3 levels to the 2.5<sup>th</sup> percentile (for chronological age) was significantly higher in group 1 ([IGF-1 (54.5% vs. 26.2%,  $p = 0.016$ )], [IGF BP3 (30.0% vs. 0%,  $p = 0.007$ )] (Table 1).

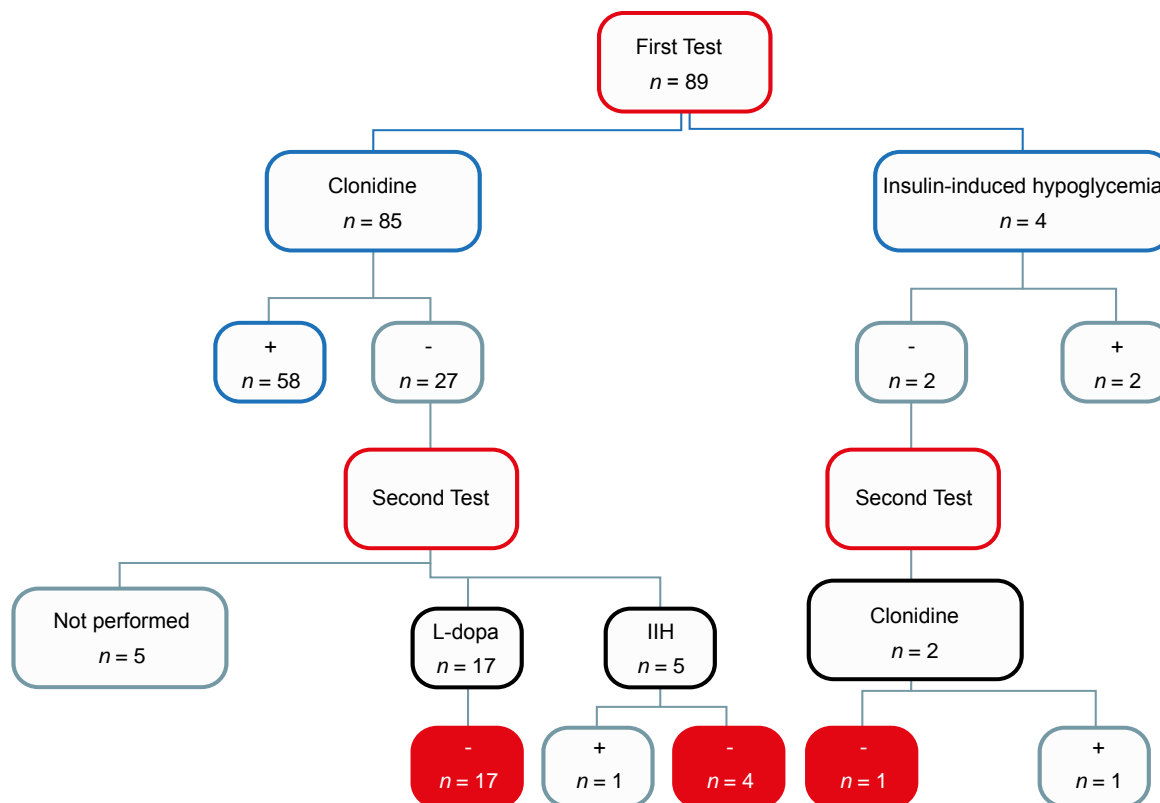


Figure 1 – Distribution of our group of patients by type and number of stimulation tests

+ positive stimulation test (peak GH level  $\geq 7$  ng/ml); - negative stimulation test (peak GH level  $< 7$  ng/ml); IHH – insulin-induced hypoglycemia.

In patients who underwent both tests, GH peak values showed a moderate correlation between each other ( $r = 0.593$ ,  $p = 0.01$ ) (Fig. 2).

The model 1 of logistic regression showed that in patients with IGF-1 levels below the 2.5<sup>th</sup> percentile, GHD was 3.4 times more likely when compared to those with IGF-1 levels above that (Table 2). However, in model 2, height (z-score) and GH secretion peak-adjusted, IGF-1 levels were not predictive. Height (z-score) and peak GH in the first test showed predictive value for GHD diagnosis, in other words, as they increased the less the likelihood of GHD (Table 2).

## DISCUSSION

The diagnosis of GHD in children is frequently a demanding clinical challenge.<sup>7</sup> In practice, in many patients, an accurate diagnosis is only possible after the final height is reached and GH secretion re-evaluation has been carried out.

Several confirmation methods have been suggested for GHD, among them physiological and pharmacological GH<sup>5,6,17</sup>, IGF-1 and IGFBP<sup>18,19</sup> stimulation tests.

Pharmacological stimulation tests, despite their known limitations (non-physiological stimulation, arbitrary cut-offs, intra-individual variation on the response to the drug),<sup>20,21</sup> remain the most consensual method to assess GH secretion.<sup>22</sup>

Two different stimulation tests with peak GH levels  $< 10$  ng/ml in short-stature children confirm GHD diagnosis.<sup>8</sup>

However, because GH secretion may be low or absent in particular situations, the definition of a specific cut-off for GHD is difficult and arbitrary.<sup>23</sup> Cianfarani *et al.* showed that reducing the cut-off from 10 to 7 ng/ml significantly increases specificity and reduces sensitivity.<sup>23</sup> CNNHC recommendations established that idiopathic GHD should be confirmed by two stimulation tests with peak GH levels  $< 7$  ng/ml, thereafter giving support to the start of replacement recombinant GH therapy.<sup>11</sup>

Oral clonidine stimulation test was the most used in our group of patients, used in the first test in 96% of our patients. This  $\alpha$ -adrenergic drug promotes GH secretion<sup>24,25</sup> in a way which is dependent on age,<sup>26</sup> obesity and physical activity.<sup>27</sup> A single test with clonidine has an 80% positive predictive value for the confirmation of GHD, using the 10 ng/ml peak GH level as reference.<sup>8</sup>

From the 24 patients who underwent two tests, clonidine was the most used drug on the first test in 22 patients. Only one patient with a negative clonidine first test ( $< 7$  ng/ml) presented a second insulin-induced hypoglycemia positive test. The other remaining patient with a second positive test underwent an insulin-induced hypoglycemia as first test and clonidine as second test. We should note that on both patients with a positive second test, peak GH levels were below the reference level established by different authors as normal secretion (10 ng/ml).<sup>8</sup>

GHD confirmation is generally an indication for two pharmacological stimulation tests to be performed with peak GH levels below 7 ng/ml.<sup>11</sup> However, a single

**Table 1** – Descriptive analysis of children and adolescents who underwent stimulation tests with (Group 1) and without (Group 2) GHD confirmation

		Group 1	Group 2	
		n = 22	n = 62	
		n (%)	n (%)	valor de p
Gender	Male	13 (59.1)	44 (71.0)	0.305
Puberty stage	I	15 (71.4)	39 (79.0)	0.717
	II	5 (23.8)	7 (14.3)	
	III	1 (4.8)	2 (4.1)	
	IV	0 (0)	0 (0)	
	V	0 (0)	1 (2.0)	
IGF1	< P2.5	12 (54.5)	16 (26.2)	<b>0.016</b>
IGF BP3	< P2.5	3 (30.0)	0 (0)	<b>0.007</b>
Δ CA/BA	CA-BA > 24 months	10 (45.5)	17 (27.4)	0.120
		<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>p-value</b>
Age	years	9.4 (3.3)	9.7 (3.0)	0.683
Height	z-score	-2.87 (0.6)	-2.09 (0.9)	<b>0.001</b>
Height (adjusted TH)	z-score	-1.50 (1.0)	-0.99 (1.1)	0.055
GV	z-score	-2.22 (1.6)	-1.26 (2.4)	0.067
BMI	z-score	-0.23 (1.1)	-0.21 (2.9)	0.944
Peak GH level (1 <sup>st</sup> test)	ng/mL	4.0 (2.1)	16.1 (6.5)	<b>0.001</b>
Δ CA/BA	months	22.7 (15.7)	15.7 (17.2)	0.099

SD: standard deviation; IGF1: insulin growth factor 1; IGF BP3: insulin growth factor binding protein 3; P2.5: 2.5th percentile; CA: chronological age; BA: bone age; GH: growth hormone; TH: target height; GV: growth velocity; BMI: body mass index.

stimulation test is enough in patients with GHD criteria and a known aetiology (central nervous system and genetic malformations).<sup>7,11,28</sup> In our study, a second test was not performed in four of the five patients with GHD with a known aetiology (and a first negative stimulation test).

Despite IGF-1 and IGFBP-3 determination being considered helpful for the confirmation of the diagnosis of GHD in children and adolescents,<sup>29-31</sup> its usefulness and predictive value are not always consensual.<sup>23,32</sup> Studies in this area have found that both parameters do not discriminate idiopathic short-stature children from those with GHD.<sup>23</sup> In the present study, IGF-1 levels adjusted for height and peak GH level in a first test, does not show any predictive value for the diagnosis of GHD.

Height (z-score) and peak GH level on the first test were the parameters with predictive value for GHD. As previously referred, all patients with a first negative test showed peak GH level < 10 ng/ml in the second test. Therefore, it seems reasonable to suggest that auxological criteria related to a negative test may be enough for the diagnosis of GHD. The importance of auxology in the diagnosis of GHD is taken to

its extreme, like for instance in Australia, where the selection of patients for replacement recombinant GH therapy is only based on auxological parameters.<sup>33,34</sup> In this respect, a word of caution is introduced by an American study that showed no differences in height, BMI and growth velocity between idiopathic short-stature and children with GHD.<sup>35</sup>

## CONCLUSION

Stimulation tests are a useful instrument for the diagnosis of GHD and should be added to clinical and auxological parameters already in use.

## CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

## FINANCIAL SOURCES

The authors declare that there was no financial gain for writing this manuscript.

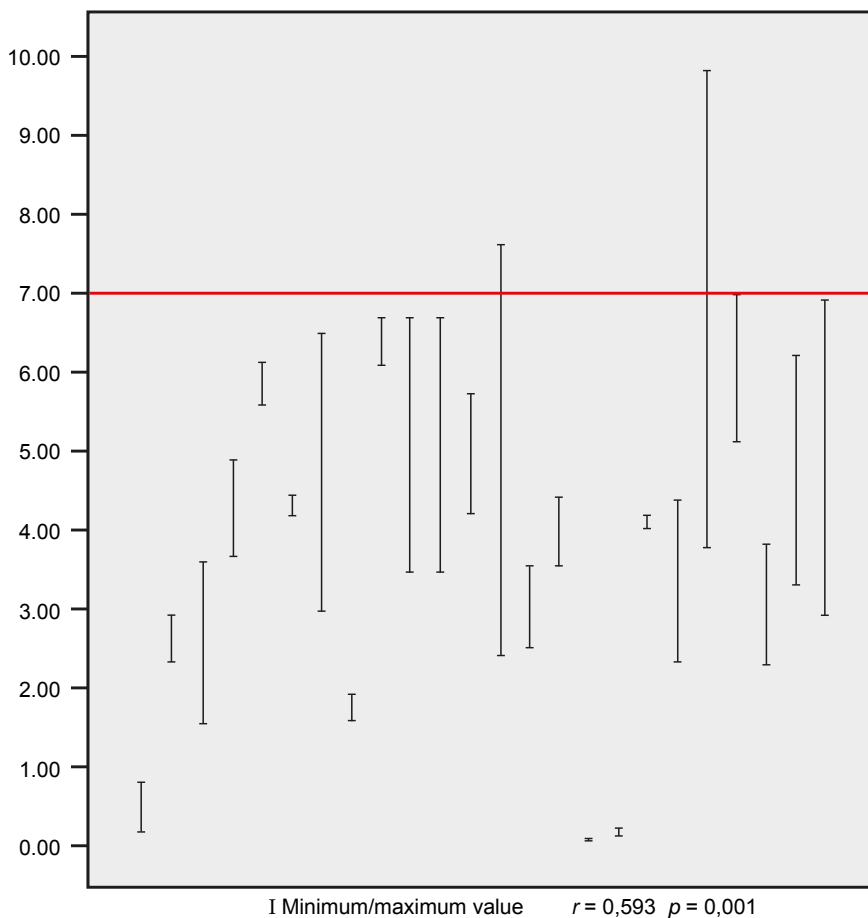


Figure 2 – Peak GH level variation (ng/ml) in patients who underwent two stimulation tests

Table 2 – Predictors of GHD confirmed by stimulation tests

Model	Variables	OR [95%CI]	p-value
1	IGF1 (< P2.5)	3.4 [1.2 - 9.3]	<b>0.019</b>
	IGF1 (< P2.5)	1.1 [0.1 - 16.0]	0.954
2	Height (z-score)	0.1 [0.1 - 0.8]	<b>0.036</b>
	Peak GH level	0.3 [0.1 - 0.7]	<b>0.005</b>

OR: odds ratio; CI: confidence interval; IGF1: insulin growth factor 1; P2.5; 2.5th percentile; GH: growth hormone; 1 – unadjusted model; 2 – height-adjusted (z-score) and peak GH level-adjusted model

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Av. Almirante Gago Coutinho, 151  
1749-084 Lisboa, Portugal.

Tel: +351 218 428 215

E-mail: [submissao@actamedicaportuguesa.com](mailto:submissao@actamedicaportuguesa.com)

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