Reappraisal of serum insulin-like growth factor-I (IGF-1) measurement in the detection of isolated and combined growth hormone deficiency (GHD) during the transition period

Reavaliação da dosagem sérica do fator de crescimento insulina-símile-1 (IGF-1) para o diagnóstico da deficiência isolada e combinada de hormônio de crescimento no período de transição

Cesar L. Boguszewski[1], Claudio Silva de Lacerda[1], Luiz de Lacerda Filho[1], Julienne A. R. de Carvalho[2], Margaret C. S. Boguszewski[2]

ABSTRACT

Objective: To evaluate the accuracy of serum IGF-1 in the detection of isolated (IGHD) or combined growth hormone deficiency (CGHD) at the transition phase. **Subjects and methods:** Forty nine patients with GHD during childhood [16 with IGHD (10 men) and 33 with CGHD (24 men); age 23.2 ± 3.5 yrs.] were submitted to an insulin tolerance test (ITT) with a GH peak < 5 μg/L used for the diagnosis of GHD at the transition phase. Pituitary function and IGF-1 measurements were evaluated in the basal sample of the ITT. Transition patients were reclassified as GH-sufficient (SGH; n = 12), IGHD (n = 7), or CGHD (n = 30). **Results:** Five (31%) patients with IGHD and 32 (97%) with CGHD at childhood persisted with GHD at retesting. One patient with IGHD was reclassified as CGHD, whereas 3 patients with CGHD were reclassified as IGHD. Mean GH peak was 0.2 ± 0.3 μg/L in the CGHD, 1.3 ± 1.5 μg/L in the IGHD, and 18.1 ± 13.1 μg/L in the SGH group. Serum IGF-1 level was significantly higher in the SGH (272 ± 107 ng/mL) compared to IGHD (100.2 ± 110) and CGHD (48.7 ± 32.8) ($p < 0.01$). All patients reclassified as CGHD, 86% reclassified as IGHD, and 8.3% reclassified as SGH had low IGF-1 level, resulting in 97.3% sensitivity and 91.6% specificity in the detection of GHD at the transition period; the cutoff value of 110 ng/mL showed 94.5% sensitivity and 100% specificity. Mean IGF-1 values did not differ in IGHD or CGHD associated with one, two, three, or four additional pituitary deficiencies. **Conclusion:** IGF-1 measurement is accurate to replace ITT as initial diagnostic test for IGHD and CGHD detection at the transition phase. Arq Bras Endocrinol Metab. 2013;57(9):709-16

Keywords

Growth hormone; somatotropin; growth hormone deficiency; transition to adult care; insulin-like growth factor I, somatomedin C; hypopituitarism

RESUMO

Objetivo: Avaliar a acurácia da dosagem sérica de IGF-1 no diagnóstico da deficiência de hormônio de crescimento isolada (DGHI) ou combinada (DGHC) na fase de transição. **Sujeitos e métodos:** Quarenta e nove pacientes com DGH na infância [16 DGHI (10 homens) e 33 DGHC (24 homens); idade 23,2 ± 3,5 anos] realizaram teste de tolerância à insulina (TTI), com pico de GH < 5 μg/L considerado diagnóstico de DGH na transição. Função hipofisária e níveis de IGF-1 foram determinados na amostra basal do TTI e os pacientes foram reclassificados em GH suficientes (SGH; n = 12), DGHI (n = 7) ou DGHC (n = 30). **Resultados:** Cinco (31%) pacientes com DGHI e 32 (97%) com DGHC na infância persistiram com DGH no reteste. Um paciente com DGHI foi reclassificado como DGHC e três com DGHC como DGHI. Os picos médios de GH foram 0,2 ± 0,3 μg/L (DGHC), 1,3 ± 1,5 μg/L (DGHI) e 18,1 ± 13,1 μg/L (SGH). O nível médio de IGF-1 foi maior no grupo SGH (272 ± 107 ng/mL) comparado com DGHI (100,2 ± 110) e DGHC (48,7 ± 32,8) ($p < 0,01$). IGF-1 baixo foi observado em todos os pacientes reclassificados como DGHC, 86% dos DGHI e 8,3% dos SGH, resultando em sensibilidade de 97,3% e especificidade de 91,6% para detecção de DGH na transição; valor de corte de 110 ng/mL mostrou 94,5% sensibilidade e 100% especificidade. O nível médio de IGF-1 foi similar nos pacientes com DGHI ou DGHC com uma, duas, três ou quatro deficiências hipofisárias associadas. **Conclusão:** A dosagem sérica de IGF-1 mostrou-se acurada para substituir o TTI na detecção tanto de DGHI como DGHC na transição. Arq Bras Endocrinol Metab. 2013;57(9):709-16

Descritores

Hormônio do crescimento; somatotropina; deficiência de hormônio do crescimento; transição para a vida adulta; fator de crescimento insulina-símile I; somatomedina C; hipopituitarismo

[1] Endocrine Division (SEMPR), Department of Internal Medicine, Universidade Federal do Parana (UFPR), Curitiba, PR, Brazil
[2] Department of Pediatrics, UFPR, Curitiba, PR, Brazil

Correspondence to:
Cesar Luiz Boguszewski
SEMPR, Serviço de Endocrinologia e Metabologia, Hospital de Clínicas, Universidade Federal do Paraná
Av. Agostinho Leão Junior, 285
80030-110 – Curitiba, PR, Brazil
cesarluiz@hc.ufpr.br

Received on Apr/13/2013
Accepted on Aug/13/2013

INTRODUCTION

Growth hormone deficiency (GHD) in adults is associated with increased adiposity, adverse serum lipid profile, reduced exercise capacity, reduced bone mineral density, reduced insulin sensitivity, decreased psychological well-being, and poor quality of life. GH replacement therapy is approved for adults with severe GHD based on its favorable impact in metabolic indices, cardiovascular risk factors, body composition, and quality of life (1-3). As a consequence, it is now recognized that some patients with childhood-onset GHD (CO-GHD) may need to continue GH replacement during adulthood to achieve full somatic development and to avoid GHD-associated morbidities (4,5).

The diagnosis of isolated (IGHD) or combined GHD (CGHD) in the pediatric population can be straightforward in children with severe and precocious growth retardation and a well-defined hypothalamic-pituitary disease, such as genetic defects (*PIT-1*, *PROP-1*, *GH*, *GHRH-R*), congenital hypopituitarism or tumors (craniopharyngiomas, pituitary adenomas). In this group, there is a high likelihood of GHD persistence in adult life (1-5). This contrasts with the diagnosis of idiopathic IGHD, which is usually based on arbitrary cutoff levels in GH provocative tests. Studies have shown that many children with this diagnosis are no longer GHD when retested at the transition phase (6-9), a period arbitrarily defined as starting in late puberty and ending with full adult maturation, lasting approximately 6-7 years after achievement of final height (10). Retesting during the transition phase usually involves GH stimulation with insulin-induced hypoglycemia and measurement of serum insulin-like growth factor-1 (IGF-1) levels (1-5).

In adults, severe GHD is defined as a GH peak < 3 µg/L in the insulin tolerance test (ITT), which is the diagnostic test of choice (1,2). However, this cutoff point was considered too restrictive for the diagnosis of permanent GHD in the transition period, and a GH peak < 5 µg/L was proposed as the diagnostic criterion (10). Similarly, it has been stated that IGF-1 value ≤ -2 standard deviation score (SDS) when the patient is off GH treatment for at least 4 weeks should be considered sufficient for the diagnosis in patients with a high likelihood of persistent GHD (1,2,10). However, the guidelines have drawn attention to the need for reassessment of established cutoffs levels in different GH tests according to specific parameters. Moreover, important questions remain on the normal reference ranges for IGF-1 and its diagnostic role in patients with low likelihood of permanent GHD (1-5,10).

In the present study, we hypothesized that determination of serum IGF-1 level would be sufficient to detect all patients with IGHD and CGHD in the transition phase, eliminating the need for GH-stimulating tests. We reviewed the records of all patients in our institution treated with GH for short stature since 1996. A cohort of young adult patients, who were treated with GH during childhood with diagnosis of IGHD or CGHD and were off GH therapy for at least 6 months, was identified and invited to participate in a cross-sectional study. We investigated the prevalence of persistent GHD in the transition phase, and examined the diagnostic accuracy of serum IGF-1 levels.

PATIENTS AND METHODS

Study protocol

A retrospective analysis of 720 records from patients treated with recombinant GH for short stature in the Pediatric Endocrine Unit of our institution since 1996 was carried out [Pediatric Phase]. Medical records were reviewed with emphasis on clinical data in the period of GH treatment, including etiology, GH tests performed for diagnostic purposes, IGHD *versus* CGHD, weight and height before and at the end of treatment, time and dose of GH, and the use of other medications. We excluded 629 patients who received GH for idiopathic short stature, Turner syndrome, intrauterine growth retardation, chronic renal failure, and genetic disorders. From the remaining subjects, we selected patients for the cross-sectional study based on [1] chronological age at the time of the study varying from 18-30 years; [2] previous therapy with GH for at least 1 year; and [3] discontinuation from GH therapy for at least 6 months. Ninety-one patients who fulfilled these criteria were identified, but forty-two were not localized or refused to participate. Thus, the final group consisted of 49 patients with CO-GHD who were selected for the cross-sectional part of the study [Transition Phase] (Figure 1).

The participants were submitted to clinical assessment, anthropometric analysis, and blood sampling for biochemical measurements, including glycemia, IGF-1, total and free T4, TSH, cortisol, prolactin, LH, FSH, testosterone (males), and estradiol (females). All par-

ticipants were submitted to an ITT for glucose and GH measurements, and a GH peak < 5 µg/L in the presence of hypoglycemia was considered for diagnosis of GHD in the transition phase (6). According to their response on the ITT and their pituitary function, patients were reclassified as GH-sufficient (SGH), isolated GHD (IGHD) or combined GHD (CGHD) (Figure 1). The study was approved by the Ethics Committee on Human Research of our institution. The protocol was fully explained and an informed consent form was signed by all participants.

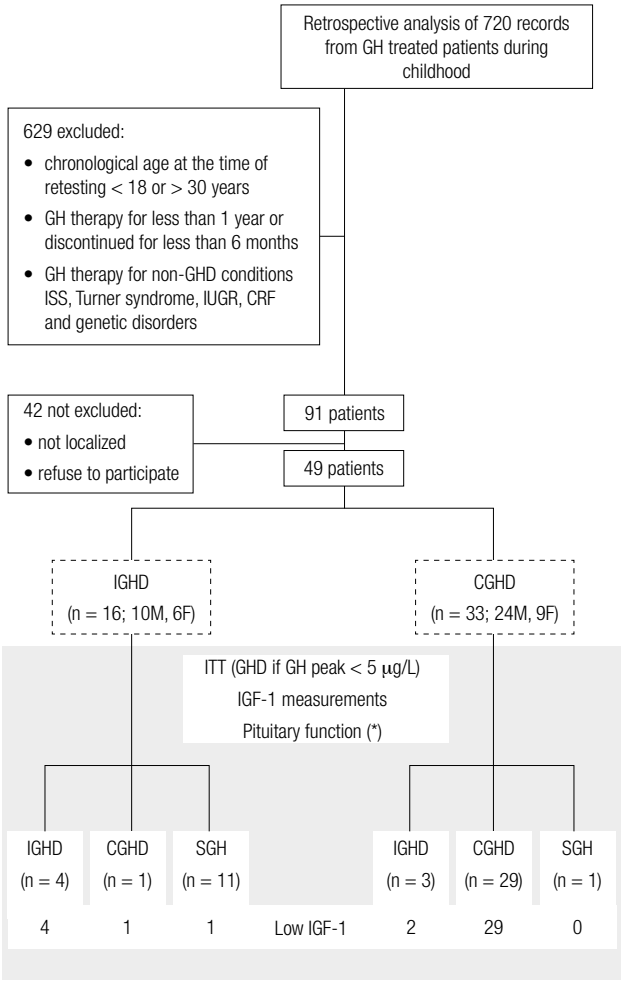

Figure 1. Study protocol. Traced lines refer to the diagnosis made at childhood (retrospective analysis of the pediatric phase). The grey area shows the cross-sectional part of the study carried out during the transition period. Asterisk refers to serum measurements of total and free T4, TSH, cortisol, prolactin, LH, FSH, testosterone (males), and estradiol (females). *ISS*, idiopathic short stature; *IUGR*, intrauterine growth retardation; *CRF*, chronic renal failure; *IGHD*, isolated growth hormone deficiency; *CGHD*, combined growth hormone deficiency; *SGH*, sufficient of GH; *ITT*, insulin tolerance test.

Insulin tolerance test (ITT) and IGF-1 sampling

ITT was performed between 8 and 9 am, after an overnight fasting. An IV heparin locked line was placed in one forearm vein, and samples for blood glucose, cortisol, and GH were collected at time 0, 15, 30, 45, 60, 90, and 120 min after soluble insulin IV administration (0.1-0.15 IU/kg). The test was considered appropriate when blood glucose reached values ≤ 40 mg/dL (2.22 mmol/L) or values lower than 50% of baseline. Serum IGF-1 was determined in the blood sample collected at time 0, as well as other biochemical measurements. All collected samples were centrifuged at 4°C, and plasma was separated and stored at -20°C for subsequent measurements.

Assays

Glycemia determination was performed automatically with a hexokinase catalyzed-glucose oxidase method. IGF-1, GH, TSH, LH, FSH, total, and free T4, testosterone, estradiol, cortisol, prolactin were measured by chemiluminescent immunometric assay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA). The sensitivity of the GH assay was 0.01 µg/L using the IRP 98/574. The inter- and intra-assay coefficients of variation were 4.2-6.6 and 2.9-4.6%, respectively, at GH levels of 2.6-17 µg/L. The sensitivity of the IGF-1 method was 2.6 nmol/L, with inter- and intra-assay coefficients of variation of 7.1% and 3.4%, respectively.

Statistical analysis

All descriptive statistical results are presented as means ± SD, unless otherwise stated. The Student *t* test was applied to investigate possible differences between continuous variables of symmetrical distribution and the Mann-Whitney test for those with asymmetric distribution. ANOVA was used for repeated measurements. The frequencies of categorical variables were estimated by Fisher's exact test. Correlations were determined by Pearson's correlation coefficient. P-value less than 0.05 was considered significant. Statistical analyses were performed using Statistica® (Statsoft Inc, Oklahoma, USA).

RESULTS

Pediatric phase – Retrospective analysis

During childhood and adolescence, 16 patients (32.6%, 10 men and 6 women) were diagnosed with IGHD and

33 (67.4%, 24 men and 9 women) were diagnosed with CGHD. The CGHD was associated with one pituitary deficiency in 6 cases, two in 9 cases, three in 13 cases, and four deficiencies in 5 cases. TSH, LH/FSH and ACTH deficiencies were present in 30, 26, and 12 patients, respectively, while 8 patients had central diabetes insipidus. In only 4 patients, GHD was secondary to an identifiable pathology, including craniopharyngioma, Langerhans cell histiocytosis, post-resection of an optic nerve glioma, and previous head and neck radiotherapy. All the remaining patients had the diagnosis of idiopathic congenital hypopituitarism.

Computed tomography and/or magnetic resonance were available for 41 patients. In the CGHD ones, twelve abnormalities were found, including anterior pituitary hypoplasia (n = 10), empty sella (n = 1), Rathke cyst (n = 1), post-surgical alterations (n = 1), and absence of the hyperintense signal of neurohypophysis (n = 1), whereas only two alterations were observed in patients with IGHD: anterior pituitary hypoplasia (n = 1) and empty sella (n = 1). At the time of diagnosis, median height z-score of the CGHD group was significantly lower than that of IGHD group (-4.2 *vs.* -2.5; $p < 0.005$), with no differences regarding age, weight and BMI (Table 1). During follow-up, GH dose did not differ between the groups, but the median time of GH treatment was significantly higher in the CGHD group (4.1 *vs.* 3 yrs.; $p < 0.03$). At the end of GH treatment, patients with CGHD were older than those with IGHD (18.4 ± 2.3 *vs.* 16.0 ± 1.3 years; $p < 0.001$), with no difference in height z-score (median -1.5, range -4.7 to 0.81 *vs.* -1.1, range -5.0 to -0.08) (Table 1).

All patients were submitted to two GH stimulation tests at the pediatric phase: ITT and clonidine. In the ITT, mean (± SD) GH peak was 1.1 ± 1.4 µg/L in the CGHD (GH peak < 3 µg/L in 32 cases and between 3-5 µg/L in 2 cases) and 3.4 ± 3.8 µg/L in the IGHD (GH peak < 3 µg/L in 10 cases, between 3-5 µg/L in 1 case and between 5-10 µg/L in 4 cases). In the clonidine test, mean GH peak was 1.5 ± 1.5 µg/L in the CGHD (GH peak < 3 µg/L in 27 cases, between 3-5 µg/L in 5 cases and between 5-10 µg/L in 2 cases) and 4.9 ± 4.4 µg/L in the IGHD (GH peak < 3 µg/L in 4 cases, between 3-5 µg/L in 5 cases, between 5-10 µg/L in 5 cases and > 10 µg/L in 1 case).

Transition phase – Cross-sectional study

At the time of retesting, mean age of the women was 21.4 ± 3.5 yrs. (range 17-27), mean weight was 51.8 ± 9.7 kg, mean height was 155 ± 6.7 cm, median (range) height z-score was -1.1 (-3.8/-0.25), and mean BMI was 21.5 ± 3.7 kg/m². For men, mean age was 23.1 ± 3.4 yrs. (range 17-31), mean weight was 59.9 ± 12.8 kg, mean height was 165.2 ± 11.1 cm, median (range) height z-score was -1.5 (-4.5/0.5), and mean BMI was 22.0 ± 4.5 kg/m². In relation to the end of GH treatment, there was a mean height increment of 5.2 cm in men and 3.7 cm in women. After retesting and interpretation of the pituitary function tests, patients were reclassified into three groups: SGH, GH peak > 5 µg/L (n = 12; 24.5%); IGHD, GH peak < 5 µg/L, and no other pituitary deficiency (n = 7; 14.5%); and CGHD, GH peak < 5 µg/L plus at least one additional pituitary deficiency (n = 30; 61%) (Figure 1 and Table 2). Of the 16 patients with IGHD at childhood, only 5 (31%) persisted with GHD, while 11 (69%) had a GH peak > 5 µg/L in the ITT and did not fulfill the diagnostic criteria for GHD in the transition phase. In contrast, thirty-two (97%) patients with diagnosis of CGHD at childhood had persistent GHD, and only 1 (3%) was reclassified as SGH due to a GH peak > 5 µg/L in the ITT.

Table 1. Main features of patients with isolated (IGHD) and combined GH deficiency (CGHD) at diagnosis and at the end of GH treatment in the pediatric phase

	IGHD (n = 16)	CGHD (n = 33)	P value
Sex (M:F)	10:6	24:9	NS
Age (yrs.)	10.8 ± 2.8	10.3 ± 3.6	NS
Height (cm)	122.2 ± 16.1	112.6 ± 17.0	NS
Height (z-score)	-2.5 (-6.2/-1.7)	-4.2 (-7.9/-2.2)	< 0.005
Weight (kg)	26.5 ± 9.8	22.1 ± 8.4	NS
BMI (kg/m²)	17.0 ± 2.9	16.8 ± 2.1	NS
BMI (z-score)	-0,25 (-2,6/3,6)	-0,22 (-2,82/1,9)	NS
GH peak ITT			
< 3 µg/L (n)	11	31	
3-5 µg/L (n)	1	2	
> 5 µg/L (n)	4	0	
GH peak clonidine			
< 3 µg/L (n)	5	26	
3-5 µg/L (n)	5	5	
5-10 µg/L (n)	5	2	
> 10 µg/L (n)	1	0	
GH therapy (yrs.)	3.0 (1.0/10.5)	4.1 (1.0/10.4)	< 0.03
Age at the end of GH therapy (yrs.)	16.0 ± 1.3	18.4 ± 2.3	< 0.001
Height (z-score) at the end of GH therapy	-1.1 (-5.0/-0.08)	-1.5 (-4.7/0.81)	NS

Values are means ± SD, except for BMI and height z-score, which are presented as medians and ranges. BMI: body mass index; ITT: insulin tolerance test; NS: not significant.

Table 2. Main features of patients with isolated (IGHD), combined GH deficiency (CGHD) or GH-sufficient (SGH) at retesting in the transition phase

	IGHD (n = 7)	CGHD (n = 30)	SGH (n = 12)
Age (yrs.)	23.4 ± 3.1	24.4 ± 3.5	21.0 ± 2.8*
Height (cm)	154.6 ± 10.8	163.0 ± 11.4	164.3 ± 6.9
Weight (kg)	50.0 ± 11.7	59.9 ± 12.4	55.6 ± 10.5
BMI (kg/m^2)	20.8 ± 3.4	22.7 ± 4.8	20.5 ± 2.8
Height (z-score)	-2.3 (-3.6/-0.5)	-1.27 (-6.7/0.5)	-0.96 (-2.9/-0.2)
GH peak ITT			
< 3 µg/L (n)	6	30	0
3-5 µg/L (n)	1	0	0
5-10 µg/L (n)	0	0	3
>10 µg/L (n)	0	0	9
GH peak ITT (µg/L)	1.3 ± 1.5	0.2 ± 0.3	18.1 ± 13.1***
IGF-1 (ng/mL)	100.2 ± 110	48.7 ± 32.8	162.1 ± 49.6**
Low IGF-1 (n)	6	30	1

Values are means ± SD, except for height z-score, which is presented as median and range.
* p < 0.05; ** p < 0.01; *** p < 0.001 *vs.* IGHD and CGHD.

At retesting with ITT, mean GH peak was 0.2 ± 0.3 µg/L in the CGHD, 1.3 ± 1.5 µg/L in the IGHD and 18.1 ± 13.1 µg/L in the SGH group (GH peak between 5-10 µg/L in 3 cases and > 10 µg/L in 9 cases). Only one patient was reclassified as GHD had a GH peak between 3-5 µg/L, with all others presenting a GH peak < 3 µg/L. Among patients reclassified as CGHD, one, two, three, or four additional pituitary deficiencies were found in 5, 7, 13 and 5 cases, respectively, with 28 having TSH deficiency, 27 with LH/FSH deficiency, 16 with ACTH deficiency, and 7 with diabetes insipidus.

One patient with diagnosis of IGHD in the pediatric phase was reclassified with CGHD (TSH and LH/FSH deficiencies) at the transition phase. Eleven patients of this group showed normal GH response (SGH) in the retest with ITT. In three patients, the initial diagnosis of CGHD at childhood was changed to IGHD at transition: two GHD girls and one GHD boy who received estrogens and testosterone, respectively, for assumption of associated hypogonadism that was not confirmed in the reevaluation. One patient with CGHD was reclassified as SGH: at childhood, he was diagnosed with GHD (GH peak ITT = 1.3 µg/L and clonidine = 0.7 µg/L), central hypothyroidism (normal-low free T4 levels) and diabetes insipidus, secondary to Langerhans cell histiocytosis. He was treated with chemotherapy for 2 years and received GH for 6 years. At retesting, his GH peak was 12 µg/L and his IGF-1 was normal.

IGF-1 measurements in the transition phase

Mean serum IGF-1 levels in the GHD patients were 59.6 ± 59.2 ng/mL (IGHD = 100.2 ± 110 ng/mL; CGHD = 48.7 ± 32.8 ng/mL), values significantly lower than those observed in the SGH group (272 ± 107 ng/mL; p < 0.01) (Table 2 and Figure 2). IGF-1 levels were low in 36 of 37 (97.3%) patients with GH peak < 5 µg/L in the ITT, and in only 1 out of 12 SGH patients (8.3%) with GH peak > 5 µg/L. All patients reclassified as CGHD, 6 of 7 (86%) reclassified as IGHD and 1 of 12 (8.3%) reclassified as SGH had low IGF-1 level, resulting in a sensitivity of 97.3%, specificity of 91.6%, positive predictive value of 97.3% and negative predictive value of 91.6% in GHD detection in the transition phase.

From the 16 patients with IGHD at childhood, eleven were reclassified as SGH and IGF-1 level was low in only one case; in the remaining five patients, IGF-1 level was low in all of them (Figure 1). Thus, in patients with diagnosis of IGHD at childhood, IGF-1 measurements exhibited 100% sensitivity and 91% specificity in GHD detection at transition phase. Of the patients with CGHD at childhood, only one was reclassified as SGH, and in this case IGF-1 level was normal. Of the remaining 32 patients who persisted with GHD, IGF-1 was low in all of them, except in one case (Figure 1). Consequently, the sensitivity and specificity of IGF-1 measurements in the detection of GHD at transition in patients with CGHD at childhood was 97% and 100%, respectively. Mean IGF-1 values did not differ in patients with IGHD and those with CGHD associated with one, two, three or four additional pituitary deficiencies (Figure 3).

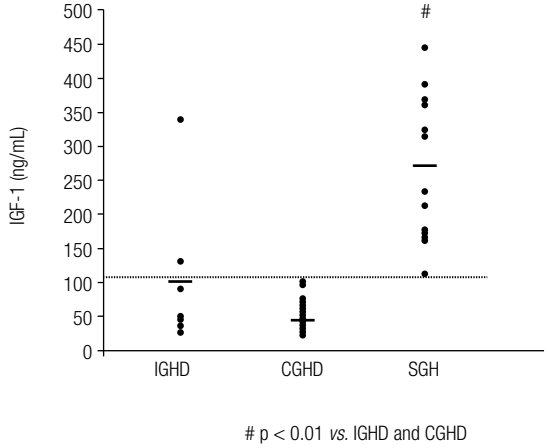

Figure 2. Serum IGF-1 levels at the transition phase in the study groups. Horizontal bars show mean levels in each category [isolated GH deficiency (IGHD), combined GH deficiency (CGHD), and GH-sufficient (SGH)]. Dashed horizontal line indicates a cutoff value of 110 ng/ml with a sensitivity of 94.5% and a specificity of 100% for GHD detection.

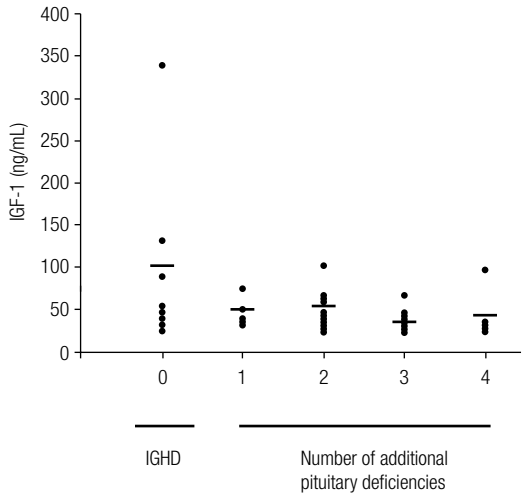

Figure 3. Serum IGF-1 levels at the transition phase, according to the number of additional pituitary hormone deficiencies. Horizontal bars show mean levels in each category. There was no significant difference among the groups.

The lowest serum IGF-1 level observed in patients reclassified as SGH was 112 ng/mL. Of the 37 patients reclassified as GHD at the transition, 35 (94.5%) presented with an absolute serum IGF-1 concentration below 112 ng/mL (Figure 2). Hence, a serum IGF-1 level < 110 ng/mL showed a sensitivity of 94.5% and specificity of 100% in the detection of GHD at the transition period.

DISCUSSION

The prevalence of persistent GHD in the transition has shown considerable discrepancy among series published in the literature, with percentages ranging from 22% to 74% depending on various factors, including the etiology, the type of GH test, cutoff values employed in the first test and in the retest, and the presence of other pituitary hormone deficiencies (11-14). The importance of this later factor was clearly demonstrated in our study, as all but one patient with CGHD at childhood had persistent GHD at retesting, compared to only 31% of those with IGHD. It is worth mentioning our patient with CGHD who was reclassified as SGH at retesting. He had Langerhans cell histiocytosis, with GHD diagnosed at childhood based on abnormal GH responses in two distinct tests, plus central hypothyroidism and diabetes insipidus. He received GH therapy during 6 years and chemotherapy for 2 years, which might explain the return of his pituitary GH secretion, although TSH and ADH deficiencies did not recover. Spontaneous recovery is also a possibility, although it was not observed in a series of eight GHD patients with Langerhans cell histiocytosis followed up for 11 years (15). Taken together, these cases show that recovery of GH secretion is not a common feature in patients with CGHD, but it is possible even in the presence of a well-established etiology.

ITT was chosen for retesting in the transition phase because it is the choice diagnostic procedure recommended by various guidelines (1-3). A statement from the European Society of Pediatric Endocrinology initially suggested a GH peak < 5 µg/L after ITT for the diagnosis of GHD at the transition phase (10). However, this cutoff value was arbitrarily adopted from data on GH responses in stimulation tests performed in normal children at late puberty. Subsequently, another statement pointed out that severe GHD in young adults should be defined as a peak GH < 6 µg/L after ITT (2), as this value showed 96% sensitivity and 100% specificity in GHD detection in a small series of 26 patients with CO-GHD and 39 controls (16). Some years later, however, the same group studied a large cohort of 79 subjects with CO-GHD and suggested that a cutoff value of 5.62 µg/L was a more accurate value for patients with high likelihood of persistent GHD (17). In the present study, we have not performed ITT in our controls, but from the 12 patients reclassified as SGH, three exhibited a peak GH between 5 and 6.1 µg/L, all with normal IGF-1 levels. The only SGH patient with low IGF-1 in our study had a GH peak of 15.5 µg/L after ITT. At the same time, only one patient with persistent GHD had a GH peak between 3 and 5 µg/L, with all others exhibiting a GH peak < 3 µg/L – which defines severe GHD in older adults (1-3). Consequently, a cutoff level of 6 µg/L would not make any difference in our results, suggesting that a GH peak of 5 µg/L on ITT is an adequate definition of permanent and severe GHD in the transition patients.

ITT and other GH stimulation tests are cumbersome procedures that might offer a considerable discomfort for the patient, might require medical supervision, and might be counterindicated in common clinical situations (1-3). Furthermore, GH tests have been challenged due to problems with reproducibility, secretagogue availability, lack of normal range values, and costs (18-20). Serum IGF-1 measurement is carried out in a simple blood sample, but it has not been considered accurate for the diagnosis of GHD in adults due to a considerable overlap with values observed in

healthy subjects (1-5). Such overlap, however, is more pronounced in adulthood-onset GHD (AO-GHD), especially after the fourth decade of life, mainly due to the physiological decline in serum IGF-1 levels associated with aging (4,21). This was clearly illustrated in a study involving 244 CO-GHD patients, in which the mean IGF-1 SDS was - 4.69 and 86% of the patients presenting serum IGF-1 level < -2 SDS, in contrast with only 52% of the older group with AO-GHD (22). For this reason, we decided to reappraise the diagnostic accuracy of IGF-1 measurement in a cohort of young adults who had been diagnosed with IGHD or CGHD at childhood, were treated with recombinant GH, and were off therapy at the time of retesting. In our study, IGF-1 measurement showed a sensitivity of 97.3% and specificity of 91.6% in the detection of GHD in transition patients. In addition, a threshold of 110 ng/mL showed 94.5% sensitivity and 100% specificity for the diagnosis in our population. In another study carried out in Brazil, serum IGF-1 level of 110 ng/mL measured by Immulite represented the - 2 SD of the normal reference range for the age range of 21-25 years (23).

In our study, all thirty patients reclassified as having CGHD were correctly identified by low serum IGF-1 level, which was below the threshold value in all cases. In patients with structural hypothalamic-pituitary abnormalities and high probability of permanent GHD, Secco and cols. demonstrated an IGF-1 < -1.78 SDS in all of their patients (17). In agreement with these findings, a recent update of The Endocrine Society Clinical Practice Guideline on adult GHD (1) stated that a low IGF-1 level at least one month off GH therapy is sufficient documentation of persistent GHD without additional provocative testing in children with structural lesions, with multiple hormone deficiencies, and those with proven genetic causes.

On the other hand, the role of IGF-1 in replacing GH tests for transition patients with low probability of permanent GHD, especially those with IGHD, is still a matter of debate (1-3). Normal IGF-1 has been reported in up to 20% in this sub-group of patients (17,22) and, according to the current guidelines, it should not rule out GHD (1-3). In our study, however, all patients with diagnosis of IGHD at childhood who persisted with GHD according to the GH responses after ITT, exhibited low IGF-1 levels. There were only two discrepancies between the GH response after ITT and IGF-1 level in our cohort of 49 patients. One male patient with IGHD at childhood who was reclassified as SGH at the transition phase based on his normal GH peak of 15.5 µg/L, showed serum IGF-1 level of 112 ng/mL, while the lowest reference limit for his age was 116 ng/mL, according to the manufacturer. The other was a female patient with CGHD at childhood, reclassified as having IGHD in the transition due to a GH peak of 1.76 µg/L in the ITT, who presented normal serum IGF-1 level of 340 ng/mL (reference range was 116-358). During adolescence, she received estrogens for assumption of associated hypogonadism, which was not confirmed in adulthood. No other pituitary deficiencies were present. It should be kept in mind that, in discrepant cases, either the response to GH after ITT or IGF-1 measurement might give false results, due a variety of factors such as age, gender, BMI, nutrition, thyroid and gonadal status, reference values, and assay variability (23-28). It has been suggested that patients with discordant values might have partial GHD (29,30), but GH therapy is not usually recommended in these cases (1,2,10).

In summary, our results show that a single determination of IGF-1 has similar sensitivity and specificity of GH response after ITT to detect GHD in the transition period (16). Thus, we believe that the determination of IGF-1 should replace ITT as initial diagnostic procedure in detecting both IGHD and CGHD in young adults. Clinical judgment must be applied for requesting ITT (or other GH test) in those few cases where IGF-1 level is within the normal range and GH therapy could be beneficial to the patient.

Disclosure: Claudio Silva de Lacerda, Luiz de Lacerda Filho and Juliene Ramires Carvalho have no conflict of interest to declare. Cesar Luiz Boguszewski, and Margaret C. S. Boguszewski received lecture honoraria, travel expenses, or consulting fees from Pfizer and Merk Serono.

REFERENCES

1. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML; Endocrine Society. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1587-609.
2. Ho KK; 2007 GH Deficiency Consensus Workshop Participants. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. Eur J Endocrinol. 2007;157:695-700.
3. Giustina A, Barkan A, Chanson P, Grossman A, Hoffman A, Ghigo E, et al. Guidelines for the treatment of growth hormone excess

and growth hormone deficiency in adults. J Endocrinol Invest. 2008;31:820-38.

4. Clayton P, Gleeson H, Monson J, Popovic V, Shalet SM, Christiansen JS. Growth hormone replacement throughout life: insights into age-related responses to treatment. Growth Horm IGF Res. 2007;17:369-82.
5. Lanes R, Boguszewski CL, Calzada R, Cassorla F, Fideleff H, Boquete H. Growth hormone deficiency: transition from adolescence to adulthood. Highlights from a Latin-American Serono Symposia International Foundation Conference. J Pediatr Endocrinol Metab. 2010;23:225-33.
6. Loche S, Bizzarri C, Maghnie M, Faedda A, Tzialla C, Autelli M, et al. Results of early reevaluation of growth hormone secretion in short children with apparent growth hormone deficiency. J Pediatr. 2002;140:445-9.
7. Maghnie M, Strigazzi C, Tinelli C, Autelli M, Cisternino M, Loche S, et al. Growth hormone (GH) deficiency (GHD) of childhood onset: reassessment of GH status and evaluation of the predictive criteria for permanent GHD in young adults. J Clin Endocrinol Metab. 1999;84:1324-8.
8. Attanasio AF, Howell S, Bates PC, Blum WF, Frewer P, Quigley C, et al. Confirmation of severe GH deficiency after final height in patients diagnosed as GH deficient during childhood. Clin Endocrinol (Oxf). 2002;56:503-7.
9. Zucchini S, Pirazzoli P, Baronio F, Gennari M, Bal MO, Balsamo A, et al. Effect on adult height of pubertal growth hormone retesting and withdrawal of therapy in patients with previously diagnosed growth hormone deficiency. J Clin Endocrinol Metab. 2006;91:4271-6.
10. Clayton PE, Cuneo RC, Juul A, Monson JP, Shalet SM, Tauber M; European Society of Paediatric Endocrinology Consensus statement on the management of the GH-treated adolescent in the transition to adult care. Eur J Endocrinol. 2005;152:165-70.
11. Longobardi S, Merola B, Pivonello R, Di Rella F, Di Somma C, Colao A, et al. Reevaluation of growth hormone (GH) secretion in 69 adults diagnosed as GH-deficient patients during childhood. J Clin Endocrinol Metab. 1996;81:1244-7.
12. Wacharasindhu S, Cotterill AM, Camacho-Hübner C, Besser GM, Savage MO. Normal growth hormone secretion in growth hormone insufficient children retested after completion of linear growth. Clin Endocrinol (Oxf). 1996;45:553-6.
13. Tauber M, Moulin P, Pienkowski C, Jouret B, Rochiccioli P. Growth hormone (GH) retesting and auxological data in 131 GH-deficient patients after completion of treatment. J Clin Endocrinol Metab. 1997;82:352-6.
14. Zucchini S, Pirazzoli P, Baronio F, Gennari M, Bal MO, Balsamo A, et al. Effect on adult height of pubertal growth hormone retesting and withdrawal of therapy in patients with previously diagnosed growth hormone deficiency. J Clin Endocrinol Metab. 2006;91:4271-6.
15. Kaltsas GA, Powles TB, Evanson J, Plowman PN, Drinkwater JE, Jenkins PJ, et al. Hypothalamo-pituitary abnormalities in adult patients with langerhans cell histiocytosis: clinical, endocrinological, and radiological features and response to treatment. J Clin Endocrinol Metab. 2000;85:1370-6.
16. Maghnie M, Aimaretti G, Bellone S, Bona G, Bellone J, Baldelli R, et al. Diagnosis of GH deficiency in the transition period: accuracy of insulin tolerance test and insulin-like growth factor-I measurement. Eur J Endocrinol. 2005;152:589-96.
17. Secco A, di Iorgi N, Napoli F, Calandra E, Calcagno A, Ghezzi M, et al. Reassessment of the growth hormone status in young adults with childhood-onset growth hormone deficiency: reappraisal of insulin tolerance testing. J Clin Endocrinol Metab. 2009;94:4195-204.
18. Popovic V, Pekic S, Doknic M, Micic D, Damjanovic S, Zarkovic M, et al. The effectiveness of arginine + GHRH test compared with GHRH + GHRP-6 test in diagnosing growth hormone deficiency in adults. Clin Endocrinol (Oxf). 2003;59:251-7.
19. Kargi AY, Merriam GR. Testing for growth hormone deficiency in adults: doing without growth hormone-releasing hormone. Curr Opin Endocrinol Diabetes Obes. 2012;19:300-5.
20. Toogood A, Brabant G, Maiter D, Jonsson B, Feldt-Rasmussen U, Koltowska-Haggstrom M, et al. Similar clinical features among patients with severe adult growth hormone deficiency diagnosed with insulin tolerance test or arginine or glucagon stimulation tests. Endocr Pract. 2012;18:325-34.
21. Corpas E, Harman SM, Blackman MR. Human growth hormone and human aging. Endocr Rev. 1993;14:20-39.
22. Lissett CA, Jönsson P, Monson JP, Shalet SM; KIMS International Board. Determinants of IGF-I status in a large cohort of growth hormone-deficient (GHD) subjects: the role of timing of onset of GHD. Clin Endocrinol (Oxf). 2003;59:773-8.
23. Rosario PW. Normal values of serum IGF-1 in adults: results from a Brazilian population. Arq Bras Endocrinol Metabol. 2010;54:477-81.
24. Clemmons DR. Consensus statement on the standardization and evaluation of growth hormone and insulin-like growth factor assays. Clin Chem. 2011;57:555-9.
25. Pokrajac A, Wark G, Ellis AR, Wear J, Wieringa GE, Trainer PJ. Variation in GH and IGF-I assays limits the applicability of international consensus criteria to local practice. Clin Endocrinol (Oxf). 2007;67:65-70.
26. Kelly JJ, Rajkovic IA, O'Sullivan AJ, Sernia C, Ho KK. Effects of different oral oestrogen formulations on insulin-like growth factor-I, growth hormone and growth hormone binding protein in post-menopausal women. Clin Endocrinol (Oxf). 1993;39:561-7.
27. Bidlingmaier M, Strasburger CJ. Growth hormone assays: current methodologies and their limitations. Pituitary. 2007;10:115-9.
28. Qu XD, Gaw Gonzalo IT, Al Sayed MY, Cohan P, Christenson PD, Swerdloff RS, et al. Influence of body mass index and gender on growth hormone (GH) responses to GH-releasing hormone plus arginine and insulin tolerance tests. J Clin Endocrinol Metab. 2005;90:1563-9.
29. Murray RD, Bidlingmaier M, Strasburger CJ, Shalet SM. The diagnosis of partial growth hormone deficiency in adults with a putative insult to the hypothalamo-pituitary axis. J Clin Endocrinol Metab. 2007;92:1705-9.
30. Tauber M, Jouret B, Cartault A, Lounis N, Gayard M, Marcouyeux C, et al. Adolescents with partial growth hormone (GH) deficiency develop alterations of body composition after GH discontinuation and require follow-up. J Clin Endocrinol Metab. 2003;88:5101-6.