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Clinical and laboratory parameters predicting a requirement for the reevaluation of growth hormone status during growth hormone treatment Retesting early in the course of GH treatment

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ABSTRACT

Objective: We aimed to define the predictive criteria, in the form of specific clinical, hormonal and radiological parameters, for children with growth hormone deficiency (GHD) who may benefit from the reevaluation of GH status early in the course of growth hormone (GH) treatment.

Design and Methods: Two hundred sixty-five children with growth hormone deficiency were retested by GH stimulation at the end of the first year of GH treatment. The initial clinical and laboratory characteristics of those with a normal (GH ≥ 10 ng/ml) response and those with a subnormal (GH < 10 ng/ml) response were compared to predict a normal GH status during reassessment.

Results: Sixty-nine patients (40.6%) out of the 170 patients with isolated growth hormone deficiency (IGHD) had a peak GH of ≥ 10 ng/ml during the retest. None of the patients with multiple pituitary hormone deficiency (MPHD) had a peak GH of ≥ 10 ng/ml. Puberty and sex steroid priming in peripubertal cases increased the probability of a normal GH response. Only one patient with IGHD who had an ectopic posterior pituitary without stalk interruption on MRI analysis showed a normal GH response during the retest. Patients with a peak GH between 5 and 10 ng/ml, an age at diagnosis of ≥ 9 years or a height gain below 0.61 SDS during the first year of treatment had an increased probability of having a normal GH response at the retest.

Conclusion: Early reassessment of GH status during GH treatment is unnecessary in patients who have MPHD with at least 3 hormone deficiencies. Retesting at the end of the first year of therapy is recommended for patients with IGHD who have a height gain of < 0.61 SDS in the first year of treatment, especially those with a normal or 'hypoplastic' pituitary on imaging. Priming can increase the likelihood of a normal response in patients in the pubertal age group who do not show overt signs of pubertal development.

1. Introduction

The diagnosis of growth hormone deficiency (GHD) is based on auxological criteria and certain biochemical tests, such as IGF-1, IGFBP-3 and GH stimulation tests. Neuroradiological findings are also valuable for its diagnosis. IGF-1 and IGFBP-3 levels can be reliable in the diagnosis of severe GHD, but normal levels of these in less severe cases will not rule out GHD [29,42]. The determination of GH status is based on pharmacologic stimulation tests using agents such as insulin, arginine, glucagon, l-dopa and clonidine. An arbitrary cut-off is used to differentiate GH sufficiency from GHD, and at the present time, a peak of > 10 ng/ml in response to stimulation is generally suggestive of GH sufficiency during childhood, whereas peaks of lower concentrations are considered to be suggestive of GHD. Stimulation tests are limited in their diagnostic accuracy due to the low sensitivity, specificity and reproducibility of the tests, in addition to the arbitrary selection of cut-off levels [19,33]. In previous reports, it has been shown that 11–83% of healthy children show a low GH response to pharmacological stimulants [14,44]. Thus, to improve sensitivity, at least two tests are required for a diagnosis of GHD. It is well known that GH secretion is a function of puberty, hormonal status (sex steroids and thyroid hormones), nutrition and body composition [1,13,37]. Growth and GH secretion both physiologically decrease in the peripubertal period, and to prevent this situation from interfering with GHD, either priming with sex steroids or retesting GH status during GH treatment is recommended.

Considering the inherent problems in the diagnostic accuracy of GH stimulation tests, it is not surprising that 25–75% of patients with a diagnosis of GHD may show normal GH responses in repeated stimulation tests after the completion of treatment [8,30]. In most studies,

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retests for a reevaluation are performed after the completion of growth in the transition period from childhood to adulthood [25,26,28,32,35]. In only a small number of studies are retests in children carried out early during GH treatment [7,9,24,41,45]. The early reevaluation of GH response may help differentiate idiopathic GHD from idiopathic short stature (ISS) and constitutional delay of growth and puberty (CDGP). The potential value of the differentiation of these conditions early in the course of GH treatment would be to either prevent unnecessary treatment or optimize the dose of GH [3].

We aimed to define the predictive criteria, in the form of specific clinical, hormonal and radiological parameters, for children with growth hormone deficiency (GHD) who may benefit from the reevaluation of GH status early in the course of GH treatment.

2. Subjects and methods

2.1. Study design

A total of 265 children (104 girls) who were receiving GH for GHD were enrolled in the study. One hundred seventy patients (64.2%) had IGHD, and the remaining 95 patients (35.8%) had MPHD. All of the patients with MPHD had at least three hormone deficiencies. The diagnosis of GHD was based on patients having a short stature with a height > 2 SD below the mean for their age and sex (CDC data as reference [22]), a decreased annual growth rate (below the 25th percentile for their age and sex [39]), a delayed bone age (BA; 2 SD below the chronological age [38]), and a peak GH in response to at least two pharmacological GH stimulation tests (L-dopa and clonidine) of < 10 ng/ml [34]. Patients with other causes for their short stature (i.e., chronic systemic disorders, celiac disease, Turner syndrome, etc.), as well as those with a history of small for gestational age and those who had a disproportionate short stature or syndromic features, were excluded from the study. A karyotype analysis ruled out Turner syndrome in all of the girls.

GH status was reassessed using pharmacologic stimulation with clonidine at the end of the first year of GH treatment to enable a first-year height velocity under treatment for the analyses. All of the patients were receiving a recombinant GH treatment (0.7 IU/kg/w–0.23 mg/kg/w) before the reevaluation of GH status. The GH treatment was stopped one week before the retest, and half of the patients were primed with sex steroids. The adherence to treatment was ensured in all of the patients by monitoring the empty vials that were brought back from each visit, which was every three months. The clinical features of the patients, i.e., age, pubertal status, height SDS, bone age, and height velocity in the first year of GH treatment, were recorded and analyzed for their impact on GH status during the retest. This study was approved by the local ethics committee, and informed consent was obtained from the patients (and/or their parents) before the study began.

2.1.1. Growth hormone stimulation tests

GH stimulation tests were performed at 8.00 a.m. after the patients fasted overnight in the euthyroid state. L-dopa (10 mg/kg; max: 500 mg) and clonidine hydrochloride (150 μg/m^2; max: 200 μg) were used in the stimulation tests during the initial evaluation for a diagnosis of GHD, whereas clonidine was used in the GH stimulation of the retest [14]. Priming with sex steroids was used in half of the peripubertal study population (boys > 12 years and girls > 10 years) prior to GH testing. A single injection of testosterone enanthate (100 mg/m^2) one week before the GH test was used for the priming in the boys, and 7 doses of ethinyl estradiol (25 mcg bid) in the last three days before the GH test were used for the priming in the girls [16].

2.1.2. Evaluation of anterior pituitary hormones

A complete evaluation of the anterior pituitary function was performed in all of the patients at diagnosis and repeated during follow-up, if deemed necessary. TSH deficiency was diagnosed by a serum free T4 level of < 12 pmol/L, and ACTH deficiency was diagnosed by a fasting serum cortisol level (taken at 8:00 a.m.) of < 3 μg/dl or peak serum cortisol level of < 19.6 μg/dl during a low-dose ACTH test [15]. A morning serum cortisol level exceeding 15 μg/dl excluded ACTH deficiency [2]. The evaluation of the hypothalamo-pituitary-gonad axis was performed primarily by clinical examination. Gonadal functions were evaluated using a measurement of the plasma sex steroids (estradiol and testosterone) and gonadotropins (FSH and LH) in patients who failed to show pubertal development until after 13 years of age in girls and after 14 years of age in boys. The boys with a low LH (< 0.3 mIU/ml) and low testosterone (< 20 ng/dl) and the girls with a low LH and estradiol (< 10 pg/ml) were followed with a possible diagnosis of hypogonadotropic hypogonadism. A prolactin level below 3.3 ng/ml was accepted as hypoprolactinemia, and a prolactin level exceeding 18.7 ng/ml was considered hyperprolactinemia.

The patients with MPHD were treated with an appropriate hormone replacement (i.e., those with hypothyroidism were treated with Na-L-T4 at a dose of 1–2 μg/kg/day, those with adrenal insufficiency were treated with hydrocortisone at a dose of 8–10 mg/m^2/day, the boys with hypogonadism were treated with testosterone enanthate at a dose of 50–250 mg/month, and the girls with hypogonadism were treated with ethinyl estradiol at a dose of 6.25–25 μg/day). Since anterior pituitary hormone deficiencies could develop over time, the anterior pituitary hormones were repeated once every six months during follow-up.

2.1.3. Auxological parameters and calculations

Standing height was measured in patients who were older than 2 years using a Harpender stadiometer that measured to the nearest 0.1 cm. Height-SDS [22] and BMI-SDS [12] were calculated using CDC (Centers for Disease Control and Prevention) charts. Bone age was assessed using the Greulich-Pyle method, and puberty was assessed using Tanner staging.

2.1.4. Imaging

Magnetic resonance imaging (MRI) of the pituitary was carried out in all of the patients. The pituitary gland was considered hypoplastic when the anterior pituitary height was < 2 SD from the normal values for the patient's age [4]. Pituitary imaging showed normal or pituitary hypoplasia in 176 patients (66.4%) and organic lesions or structural abnormalities in 89 patients (33.6%). Craniopharyngioma (25/89), Rathke cleft cyst (5/89), germinoma (1/89), pilocytic astrocytoma (1/89), Langerhans cell histiocytosis (1/89), and adenopituitary macroadenoma (3/89) were the organic pathologies that were localized in the sella and suprasellar region. There was an empty sella in six patients (6/89) and posterior pituitary localization defect (ectopic posterior pituitary (EPP) in addition to the absence of infindibulum) in 47 patients (47/89).

2.1.5. Hormone measurements

The GH levels were measured using an immunochemiluminometric assay (ICMA), which was performed on an IMMULITE 2000 System (Siemens, England). The intra- and inter-assay CVs were 3.7 and 5.7%, respectively, and the analytic sensitivity of the test was 0.01 ng/ml. The serum IGF-1 and IGFBP-3 levels were measured with the Beckman Coulter trademark assays using the immunoradiometric assay (IRMA) method. The intra- and inter-assay CVs of the IGF-1 level were 2.6 and 4.5%, respectively, with an analytical sensitivity of the test being 2 ng/ml. The intra- and inter-assay CVs of the IGFBP-3 level were 4.4 and 13.5%, respectively, with an analytical sensitivity of the test being 0.27 ng/ml. The serum IGF-1 [6] and IGFBP-3 SDSs [20] were calculated using the reference tables for age, gender, and stage of puberty. For the serum IGF-1 SDS, the formula ($IGF1^{0.4}$ − f(age)) / (SD) was used, and for the serum IGFBP-3 SDS, the formulas (IGFBP3-y) / (SD) and y = (β × age) + α were used. The serum FSH, LH and