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Assessment of serum IGF-I concentrations in the diagnosis of isolated childhood-onset GH deficiency: A proposal of the Italian Society for Pediatric Endocrinology and Diabetes (SIEDP/ISPED)

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ABSTRACT. The diagnosis of GH deficiency (GHD) is based on the measurement of peak GH responses to pharmacological stimuli. Pharmacological stimuli, however, lack precision, accuracy, are not reproducible, are invasive, non-physiological and some may even be hazardous. Furthermore, different GH commercial assays used to measure GH in serum yield results that may differ considerably. In contrast to GH, IGF-I can be measured on a single, randomly-obtained blood sample. A review of the available data indicates that IGF-I measurement in the diagnosis of childhood-onset isolated GHD has a specificity of up to 100%, with a sensitivity ranging from about 70 to 90%. We suggest an algorithm in which circulating levels of IGF-I together with the evaluation of auxological data, such as growth rate and growth, may be used to assess the likelihood of GHD in pre-pubertal children.
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INTRODUCTION

In children with short stature the diagnosis of GH deficiency (GHD) is classically established when GH concentrations do not reach an arbitrary cut-off value (usually between 7-10 µg/l) after two pharmacological stimuli (1). Although biochemical tests for GH secretion clearly distinguish children with severe GHD, recognition of more subtle forms of GH insufficiency now represents a diagnostic dilemma (2, 3). Clinical evaluation, laboratory assessment and neuroimaging findings are all helpful in narrowing the range of diagnostic uncertainty. Measurement of circulating GH-dependent growth factors, such as the IGF-I and -II, IGF binding protein-3 (IGFBP-3) and acid-labile subunit (ALS), have all been repeatedly evaluated for the diagnosis of GHD (2-6).

Herein we propose a diagnostic algorithm that combines clinical evaluation, neuroimaging and laboratory tests, focusing on the usefulness of IGF-I measurement.

BIOCHEMICAL DIAGNOSIS OF GH DEFICIENCY

The diagnosis of GHD relies on the measurement of GH peak responses to pharmacological stimuli. At present, more than 30 different provocative tests are available to test pituitary GH secretion (1). However, their use and interpretation remain controversial (1-6). Much of the difficulty in the interpretation of the results lies in the poor reproducibility of the stimulation tests (7, 8), as well as in the fact that they do not reflect spontaneous GH secretion (9, 10). In addition, the patients' response to pharmacological stimulation is not predictive of their response to GH therapy

*See appendix.

Key-words: GH deficiency, GH secretion, IGF-I, IGF-II, IGF-binding protein-3, acid-labile subunit.

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(2, 4). Finally, stimulation tests are non-physiological, invasive and sometimes may be even hazardous (2, 4). Measurement of spontaneous GH secretion offers no diagnostic advantage over pharmacological tests in the diagnosis of GHD (11).

An additional problem in the diagnosis of GHD is represented by the variability of the different commercial GH assays (12, 13). The data recently reported by Mauras et al. (14) using new sensitive GH assays provide GH levels that are 2- to 3-fold lower than those commonly measured using radioimmunoassay. This in part reflects a) the fact that human GH circulates in a variety of different isoforms and b) that many assay methods for GH measurement differ in terms of antibody specificity, assay format (ie single-antibody radioimmunoassay, immunoradiometric or chemiluminometric assays) and the choice of the reference preparation (ie pure DNA-derived 22-kDa preparation, IRR88/624, GH 22 Kda international standard, and IS/ 98/574, yield results that are reduced by 50% compared to the two pituitary-derived standard preparations IRR 66/217 and the purer IRR 80/505) (12-14).

IGF-I is mainly regulated by GH and nutrition. Other factors, such as sex steroids, thyroid hormones and chronic diseases, may also affect IGF-I concentrations. In general, when malnutrition, hypothyroidism, hypogonadism and chronic illnesses are excluded, low serum IGF-I concentrations indicate impaired GH secretion or action. Specific IGF-binding proteins (IGFBP) and an acid labile subunit (ALS) bind IGF-I to form a ternary complex that prolongs its circulating half-life and minimizes diurnal fluctuation. Thus, unlike GH, IGF-I can be measured in a single, randomly-obtained blood sample.

In the last decade, several studies have investigated the diagnostic value of IGF-I in children with suspected GHD. Between 1995 and 2005, sixteen papers reported results on the accuracy of IGF-I in the diagnosis of GHD (15-30). The results of these studies are summarized in Table 1. Most of these reported a specificity ≥90% and a sensitivity of about 70% or greater. In particular, a recent study involving 131 subjects (chronological age 1.3-25 yr), 72 carefully selected patients with childhood-onset severe GHD and 59 subjects with idiopathic short stature (30), showed that the specificity of IGF-I in children younger than 11 yr was 100% with a sensitivity of approximately 70%. Taken together, these data indicate that subnormal serum IGF-I levels strongly support a diagnosis of GHD (high specificity). On the other hand, normal IGF-I concentrations do not exclude the diagnosis of GHD in about 30% of cases.

IGFBP-3 is the major serum carrier of IGF (IGF-I and -II) and binds 95% of them. IGFBP-3 is age-dependent, increasing from early childhood through puberty. Since IGFBP-3 is GH-dependent and has a long serum half-life, it represents a stable indicator of changes in GH secretion and action, and may, theoretically, provide some advantages over IGF-I in the diagnosis of GH hyposecretory states. IGFBP-3 is, in fact, less dependent on nutritional changes, and its serum concentrations are in the mg/l range, so that the sensitivity of the assay method is not a serious drawback. Moreover, the assay does not require any extraction procedure. In the last 15 yr, 15 papers have been published on the diagnostic value of IGFBP-3 measurement in children suspected of having GHD (15-22, 24, 27-32). Taken together, the results of these studies indicate that IGFBP-3 measurement alone offers no advantage over IGF-I measurement.

IGF-II is much less GH-dependent than IGF-I (33, 34), but some reports have shown decreased levels of IGF-II in patients with GHD (33, 35, 36), suggesting that IGF-II measurement may be of help in the diagnosis of GHD. However, there is not enough evidence to support its routine clinical use.

Table 1 - *Accuracy of IGF-I measurement in the diagnosis of isolated GH deficiency (GHD).*

Author/(Ref.)	Sensitivity (%)	Specificity (%)
Cianfarani et al. (15)	75	90
Nunez et al. (16)	69	76
Juul et al. (17)	53	98
Tillman et al. (18)	34	72
Rikken et al. (19)	65	78
Mitchell et al. (20)	62	47
Weinzimer et al. (21)	73	NA
Granada et al. (22)	70	95
Bussieres et al. (23)	72	95
Ranke et al. (24)	75	32
Cianfarani et al. (25)	73	95
Lissett et al. (26)	86	NA
Das et al. (27)	86	100
Boquete et al. (28)	68	97
Jensen et al. (29)	90	NA
Cianfarani et al. (30)	69	100*

NA: not assessed. *In children <11 yr, and 68% in the older ones.

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Circulating levels of ALS, a protein that is produced by the liver, show only minimal diurnal variations and increase with age. Measurement of circulating ALS does not offer any advantage over measurement of IGF-I (37). Undetectable ALS concentrations suggest inactivation of the gene encoding for the ALS (38).

PROPOSED ALGORITHM IN THE DIAGNOSIS OF GHD

Based on the above considerations, it is apparent that measurement of IGF-I has the best accuracy in the diagnosis of GHD, particularly in pre-pubertal children. Therefore, we propose measurement of IGF-I as the initial step in the laboratory work-up of children with suspected GHD (Fig. 1). Evaluation of IGF-I concentrations, in fact, represents a useful tool for assessing the likelihood of GHD in pre-pubertal children. Thus, in pre-pubertal children with short stature, pathological growth rate and circulating IGF-I levels <–2 z-score (indicating severe GHD), brain magnetic resonance imaging (MRI) should be performed, since severe GHD is uncommon in patients with normal MRI of the hypothalamic-pituitary area (39, 40). In case of hypothalamic-pituitary abnormalities, the diagnosis of GHD is confirmed and GH replacement therapy can be started. In case of normal MRI findings, one GH provocative test should be carried out [preferably insulin-induced hypoglycemia, insulin tolerance test (ITT)]. If GH secretion is insufficient, then GH replacement therapy can be started. If the GH response to the provocative test is normal, then a careful clinical follow-up is recommended. Children with serum IGF-I levels between -1 and -2 z-score (low likelihood of GHD) should undergo a conventional diagnostic work-up based on two pharmacological GH stimulation tests. Indeed, normal IGF-I concentrations do not exclude a diagnosis of GHD in about 30% of cases (30), suggesting that in cases of slow growth, evaluation of GH secretion should be undertaken. Short children with normal growth rate (> –1 SD) evaluated for at least a 6-month observation period do not need endocrine evaluation and should be followed-up clinically only. In most countries, including Italy, a biochemical defect in GH secretion must be proved to prescribe GH replacement therapy in a short patient. This continues to be the case, even though recent advances

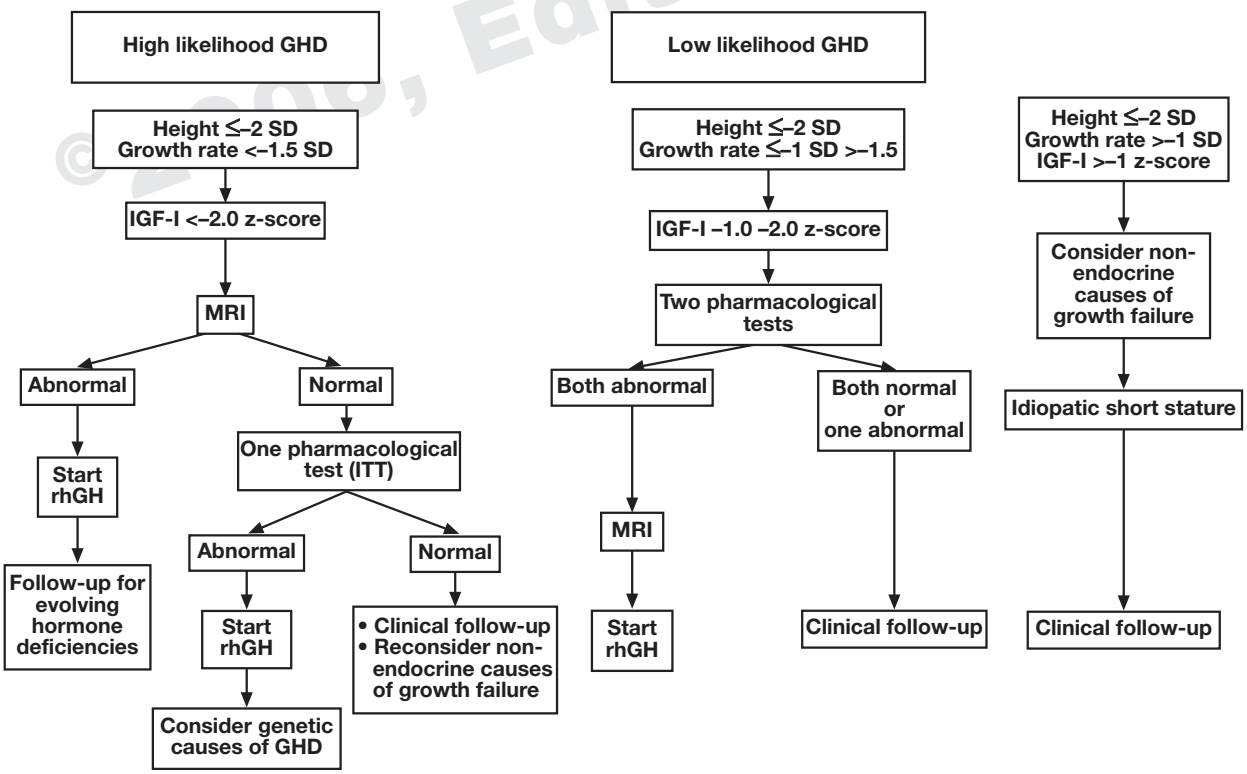

Fig. 1 - *The figure shows the algorithm according to the likelihood of GH deficiency (GHD) as suggested by the circulating levels of IGF-I (< –2 z-score or between –1 and –2 z-score, respectively). A third harm includes children with short stature, growth rate >–1SD and circulating IGF-I levels >–1 z-score. MRI: magnetic resonance imaging; ITT: insulin tolerance test; rhGH: recombinant human GH.*

indicate the need to revise diagnostic criteria. This paper aims to contribute to a redefinition of the criteria for selecting patients that are eligible to receiving treatment with GH.

APPENDIX

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