

INVITED COMMENTARY

GH releasing peptide 2 test: the holy grail of testing GH deficiency?

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Treatment of growth hormone deficiency (GHD) with GH rests on the accurate biochemical diagnosis of the condition even though clinical symptoms, signs and the assessment of risk factors may aid the diagnosis. This is particularly true for the parallel occurrence of other pituitary dysfunctions, which may simplify the procedure according to national and international guidelines (1). Due to the pulsatile nature of GH secretion, simple measurement of basal GH concentrations is not successful and only multiple sampling, clearly not practical, would help to define the GH status, especially as confounding factors such as age and sex hormone status, further influence GH levels. Insulin-like growth factor-I (IGF-1) or IGF-binding protein-3, as GH target hormones, are not pulsatile secreted but similarly modulated by confounding factors and are not diagnostic for GHD because normal levels of both factors may not preclude GHD.

Diagnosis thus rests on provocative tests for GH (2, 3). None of the currently available procedures to stimulate GH is optimal and fulfils the requirements of an ideal test e.g. fast and easy to perform, safe, economical and most importantly accurately discriminates between the normal situation and full or partial GHD. The insulin tolerance test (ITT), still regarded as the 'gold standard', exemplifies these problems. Even though unwanted effects are very rare there are reports of serious side effects. The test is contraindicated in patients with a history of coronary, cerebrovascular or any convulsive disease, and requires particular attention in the elderly (3). Expensive close supervision by experienced personnel throughout the test is therefore mandatory. The mechanism of action includes hypothalamic centres, which allow evaluating and detecting both hypothalamic and pituitary causes of GHD. Generally, the discriminatory power is high but in patients with borderline tests the reproducibility of the ITT is not sufficient (4, 5). When different provocative tests were compared in patients with multiple pituitary hormone deficiencies, where GHD can be anticipated, the best discriminatory power was found with ITT and GH-releasing hormone (GHRH)-arginine test with a sensitivity of 96% (ITT) or 95% (GHRH-arginine) and a specificity of 92 or 91% respectively. Much poorer results were described with other stimulation procedures and the performance of all tests deteriorated when fewer pituitary axes were affected (6). The GHRH-arginine test recently gained wide acceptance because of its good

tolerability, its lack of severe side effects and its high discriminatory power. However, it has been shown by Ghigo and colleagues, who originally proposed this combinational approach (7), that the test is more prone to be influenced by confounding factors such as aging or obesity (8). Furthermore, GHRH directly stimulates the pituitary, which may lead to a falsely normal GH response in patients with GHD of hypothalamic origin (9).

Another major obstacle for using these tests without local standardization procedures is the still lacking standardization of GH determinations, which does not allow us to draw general conclusions on threshold levels and to delineate the influence of confounding factors in small series. To overcome these problems we recently evaluated the most popular stimulation tests of a large international database of patients with severe GHD. In more than 1000 patients with severe GHD we found a comparable dependency on other pituitary deficiencies, on gender and age for the ITT (10).

All this clearly defines the need to search for better provocative stimuli to define GHD and to decide on GH replacement therapy. The present work of Chihara *et al.* published in this issue (11) may help in this context. The group compared ITT to stimulation with GH releasing peptide 2 (GHRP-2). The synthetic hexapeptide, also named pralmorelin, is derived from a metenkephalin peptide. It is the most potent of the family of synthetic GH stimuli known in humans and acts via the endogenous ghrelin receptor (12). As these receptors have been identified both in the hypothalamus and the pituitary, GHRP-2 action may not be restricted to the pituitary. Previous data confirmed by the recent work of Chihara *et al.* in the present issue suggest a dose-dependent and specific GH release in healthy volunteers independent of age, sex and obesity (13), and support the results of the combination tests of GHRP-2 with GHRH (14). Other data in small groups of patients with GH deficiency support these findings and show that the response is specific for the somatotrophic axis (15, 16). Chihara and co-workers compared a single i.v. GHRP-2 injection to a classical ITT in 58 subjects with severe GHD of GH < 3 µg/l to the ITT. The patient group consisted of both genders, hypothalamic and pituitary causes of GHD and varied largely in age and body weight. Seventy-seven healthy subjects with a similar variation of potentially confounding factors were used as controls. The results are very promising.

Severe GHD could be diagnosed with high reliability in all subjects using a threshold of 15 µg/l for peak GH levels which was reached 60 min after injections. The test is well tolerated. Significant side effects are hot flushes and borborygmus found in 29% of controls but in 36% of patients. Reproducibility is high and no confounding effects of age, gender or body fat are described. Despite these very encouraging results the study suffers from the limitations frequently found in GH testing. The high number of potentially important variables does not allow the drawing of a firm conclusion on the basis of the relatively low numbers studied here. This is exemplified in the author's claim that there are no differences between hypothalamic and pituitary causes of GHD. This finding may be obscured by the small group sizes and may also be further influenced by the duration of GHD. Previous reports indicate that patients with mutations of the GHRH receptor respond with a four- to fivefold GH increase over baseline induced by GHRP-2, indicating independence of the response from GHRH. When compared to healthy subjects this stimulation is grossly attenuated suggesting atrophy of somatotroph cells (16). Thus, larger series including patients with various hypothalamic and pituitary disorders as well as patient groups difficult to test in other test batteries, like patients suffering from GHD after traumatic brain injury, are still needed. Finally, the availability of the peptide for routine use is currently unsolved, as are the costs of such preparations. Nevertheless, the recent study is a promising step in the ongoing search to find the holy grail of GH testing.

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