The Diagnosis of Growth Hormone Deficiency in Adults

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Introduction

Adults with GH deficiency (GHD) have a recognisable syndrome of increased adiposity, reduced lean tissue mass and bone mineral, diminished exercise tolerance and impaired psychological well-being (1). However, neither the abnormalities of body composition and function, nor the overall features of the syndrome is sufficiently distinctive to enable a confident diagnosis of GH deficiency. Biochemical tests therefore remain necessary for diagnosis. Since GH secretion decreases with aging and is reduced by obesity (2), both these factors must be controlled for in an evaluation of diagnostic methods for GH deficiency.

Comparison of Diagnostic Tests

From an evaluation of the merits of the insulin tolerance test (ITT), mean 24 h GH concentration (IGHC, derived from repetitive sampling every 20 min), IGF-I and IGFBP-3, we have previously reported that the ITT was the only test capable of distinguishing patients with organic GHD from normal subjects matched for age, sex and BMI (3) (Fig. 1). The sensitivity of

the GH RIA used in our study (0.2 µg/L) limited the utility of IGHC since 16% of normal subjects as well as 80% of hypopituitary subjects had "undetectable" values. Using a GH ELISA with 2 order greater sensitivity (1 ng/L) (4, 5), we found that (i) IGHC was detectable in all GHD and normal subjects and (ii) there was a better but still incomplete separation of values between hypopituitary and normal subjects (iii) there was a significant correlation between IGHC and IGF-I, a relationship not demonstrable when GH was measured by RIA but showing that IGHC accounted for only 50% of the IGF-1 variance.

In the same study IGF-1 and IGFBP3 were also of limited diagnostic value because of a marked overlap in values between the hypopituitary and normal subjects, and hence low sensitivity (3). This finding can be explained by the above observation that circulating IGF-1 in GHD and normal subjects may be dependent on factors other than GH. A review of recent reports indicates overall sensitivities for IGF-I and IGFBP-3 of about 50% and 30%, respectively. More recently, we have found that measurement of the acid-labile subunit, ALS, of the IGF/IGFBP3 complex has a similar limited sensitivity to IGF-I in the diagnosis of GHD.

Evaluation of Diagnostic Tests

According to Bayes' theorem, the ability of a test to correctly identify the presence of dis-

Fig. 1 Comparison of (A) peak GH response to insulin tolerance test, (B) 24 h integrated GH concentration (IGHC), (C) IGF-1 and (D) IGFBP-3 levels in hypopituitary (●) and normal (○) subjects matched for sex, age and body mass index. Data are derived from Hoffman *et al.* (3).

Fig. 2 Relationship between IGF-1 and integrated GH concentration (IGHC) in GH deficient (●) and normal (○) subjects as measured by a supersensitive ELISA. Data are derived from Reutens *et al.* (4).

ease (positive predictive value, PPV) depends on the prior probability of disease in the population tested. On the basis of a recent Swedish study we can estimate the prevalence of organic GHD in the general population to be less than 0.02% (6). In contrast, up to 80% of patients with known pituitary disease attending an endocrine department outpatient clinic have organic GHD (7, 8). Based on current knowledge of sensitivity, specificity and prior probability of disease, the PPV of the ITT in patients with a history of pituitary disease is 99%, but less than 1% in the general population. We emphasise that although reliable in adults this test is not reliable in children because of the marked dependence of the GH response on sexual maturation (9). The ITT, although uncomfortable, is a safe test when performed in adults in an experienced endocrine unit (10). The diagnostic potential of other tests of GH stimulation needs to be systematically evaluated and should not be extrapolated from that obtained from the ITT since the GH stimulatory capacity differs between

different agents (11). Newer potent provocative agents currently under investigation such as GH releasing peptides (12) or combined pyridostigmine and GHRH, hold promise for the future as less stressful stimulation tests.

Conclusion

We conclude that GHD may be reliably diagnosed by the ITT, but should be undertaken only in adults with known or suspected pituitary disease. The merit of other stimulation tests should be investigated and not extrapolated from the ITT. IGF-1 and IGFBP-3 are unreliable indicators of GH deficiency.

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