

Overcoming the need for a second test: an evaluation of anthropometric, biochemical and radiological parameters in the diagnosis of Growth Hormone Deficiency

Muzzammil N. Ali^{1,2}; Angela Casey¹; Jeremy M.W. Kirk¹; Renuka P. Dias^{1,2}

¹Department of Paediatric Endocrinology and Diabetes, Birmingham Childrens Hospital, Birmingham, UK

²Centre for Rare Diseases and Personalized Medicine, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK



INTRODUCTION

- The prevalence of growth hormone deficiency (GHD) varies from 1:3,500 to 1:10,000¹. GHD is most commonly isolated *ie.* IGHD, although it can be combined with other pituitary hormone deficiencies (eg. MPHD, midline defects, CNS tumours and following cranial irradiation).
- There is no current consensus diagnostic gold standard for IGHD².
- Due to inherent difficulties in quantitatively assessing GH secretion and problems directly associated with provocation tests (Box 1), there is considerable variation in the degree of use and interpretation of these biochemical tests by different clinicians.

NICE 2010 guidance³ recommends that 2 growth hormone (GH) stimulation tests each demonstrating a subnormal GH peak of <6.7 µg/ml (20 mU/l) is required to confirm a diagnosis of IGHD^{4,5}.

The Consensus Guidelines from the GH Research Society⁴ in 2000 state that the diagnosis of IGHD should be based on:

- (a) clinical history and examination
- (b) auxological data
- (c) radiological evaluation (bone age and pituitary imaging)
- (d) biochemical testing of the GH-axis (*ie.* measurement of IGF-I/ IGFBP-I and by measurement of GH secretion via provocation tests)

BOX 1: PROBLEMS WITH GH PROVOCATION TESTS^{1,5}

- Poor reproducibility
- Variability of different GH assays
- Invasive
- Time consuming
- Expensive ~ £1,000 per test
- Potential risks & side effects (dependent on test): hypoglycaemia, hypotension, anaphylaxis, vomiting, nausea, hypokalaemia
- Validity: arbitrary cut off regardless of stimulus/ assay (USA <10 µg/l, UK <6.7 µg/l)
- Dependent on age, body composition, pubertal status, nutritional status, GH secretion prior to testing
- False negatives (“fail”) in prepubertal children: no consensus on sex steroid priming
- Non-physiological.

AIMS & OBJECTIVES

1. To interrogate clinical, biochemical and radiological parameters in the diagnosis of IGHD and Idiopathic Short Stature (ISS) in an attempt to reduce the need for dynamic function testing, and therefore the need for confirmatory testing.
2. To determine what proportion of children diagnosed with IGHD continue to be GH deficient after attaining their final height

METHODS

- In our centre, 3 different GH provocation tests are used: insulin tolerance (ITT), glucagon stimulation (GST) and arginine stimulation (AST).
- A retrospective review of all patients from 2002 to 2014 undergoing two tests was performed. A cut-off value of 6.7 µg/l (20 mU/l) was used to differentiate between normal and subnormal GH secretion. Those patients with two abnormal tests were compared with those with one abnormal test

RESULTS

138 patients underwent 2 GH stimulation tests; 32% (45) had a normal GH peak (>6.7 µg/l) on repeat testing and were therefore diagnosed as idiopathic short stature (ISS).

	IGHD (n=93)	ISS (n=45)	P-value
Sex (females:males)	27F:66M	13F:32M	
Mean Age at 1 st Assessment (yr.) (95% CI; SD)	8.1 (0.95-16.29; SD 4.2)	7.9 (1.09-14.1; SD 3.7)	NS
Mean Bone Age delay (yr.) (95% CI; SD)	-1.1 (-5.2-2.8; SD 1.33)	-0.86 (-5.8-1.5; SD 1.2)	NS
Low IGF-1 level [¶] (number of children, %)	37 (39.8%)	10 (22 %)	NS
HV SDS pre-test (95% CI; SD)	-0.86 (-5.9-5.1; SD 2.1)	-0.5 (-5.3-11.85; SD 3.3)	NS
HV SDS 1 yr. post-test (95% CI; SD)	2.36 (-4.3-13.6; SD 3.5)	0.6 (-5.2-7.2; 3.5)	0.016
Final Height SDS (95% CI; SD)	-0.92 (-5.6-1.8; SD 1.9)	-1.19 (-2.2-0.6; SD 0.9)	NS

IGF-I: insulin-like growth factor I, HV: height velocity, SD: standard deviation, SDS: standard deviation score, CI: confidence interval, NS: not significant.

[¶] Compared to IGF-I reference values according to Tanner stages I-V.

DISCUSSION/CONCLUSION

- A single biochemical test for the diagnosis of IGHD is not appropriate as GH secretion is a continuum between normality and abnormality. We have previously shown that there is no cut-off on a 1st GH-stimulation test that will predict an abnormal 2nd test⁶.
- Our study shows that approximately one-third of patients who undergo dynamic function testing for GHD will have a normal GH peak on a 2nd test.
- Although Cianfarani *et al.*⁷ achieved 95% sensitivity and 96% specificity in confirming the diagnosis of GHD by combining IGF-I and height velocity data, our study shows that there is no difference between IGHD vs ISS in terms of mean BA delay, IGF1 levels and pre-test HV SDS. Our data indicates that these parameters independently, or in combination, are not able to improve the pre-test probability of having a low GH peak on 2 tests.
- Whilst our study shows a significant difference in HV SDS between IGHD and ISS 1-year after dynamic testing (reflecting the effect of GH treatment in IGHD), there appears to be no significant difference in final height outcomes in either group.
- At present, undertaking 2 GH-stimulation tests appears to be the best way to distinguish IGHD from ISS, which is consistent with NICE guidance³.

REFERENCES

1. Stanley T. Diagnosis of growth hormone deficiency in childhood. *Curr Opin Endocrinol Diabetes Obes* 2012;19:47–52.
2. Van Vught AJ, Nieuwenhuizen AG, Gerver WJ, *et al.* Pharmacological and physiological growth hormone stimulation tests to predict successful GH therapy in children. *J Pediatr Endocrinol Metab* 2009;22:679–694.
3. National Institute for Health and Clinical Excellence (NICE). Guidance on the use of human growth hormone (somatotropin) in children with growth failure. Review of Technology Appraisal Guidance No. 42. 2010. (www.nice.org.uk)
4. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab* 2000;85:3990–3993.
5. Gandrud LM, Wilson DM. Is growth hormone stimulation testing in children still appropriate? *Growth Horm IGF Res* 2004;14:185–194.
6. Juma Z *et al.* GH testing: reducing the need for a second test for the diagnosis of GH deficiency. *Endocrine Abstracts* (2013) 33 OC1.1 | DOI:10.1530/endoabs.33.OC1.1
7. Cianfarani S, Tondinelli T, Spadoni GL, *et al.* Height velocity and IGF-I assessment in the diagnosis of childhood onset GH insufficiency: do we still need a second GH stimulation test? *Clin Endocrinol (Oxf)* 2002;57:161–67