

**All Wales Clinical Biochemistry Audit Group**  
**Standards for the Investigation of Short Stature in Children**

**INTRODUCTION**

Recombinant growth hormone (GH) therapy is recommended for children with a clinical diagnosis of GH deficiency (GHD) supported by height measurements and biochemical and radiological findings.<sup>1</sup> However, dynamic tests of GH reserve are potentially dangerous<sup>2</sup> and a range of screening and diagnostic tests are available, none of which are recognised as the gold standard.<sup>3</sup> The subject is also complicated by the heterogeneity of circulating GH and the variation between GH assays used for diagnostic purposes.<sup>4,5</sup> The investigation of GHD is problematic and requires consideration of all available data to make a diagnosis.<sup>6</sup>

A survey was recently undertaken in Wales using questionnaires circulated to both consultant paediatricians with an interest in childhood growth disorders and consultant clinical biochemists at all 13 Welsh hospitals where children with short stature are referred for investigation. The findings, presented at an audit meeting in March 2001, showed variations in practice in the investigation of suspected GHD. The following standards are recommended in the light of the survey findings, discussion at this meeting and previous guidelines and publications, including those from NICE.<sup>1,5-8</sup>

**STANDARDS**

**1. General Approach**

There should be a protocol for the investigation and further management of GHD, agreed between the local paediatrician with an interest in childhood growth disorders and the clinical biochemistry laboratory. GHD is primarily a clinical diagnosis, supported by measurements of height together with biochemical and radiological findings. Assessment of the GH/IGF-1 axis should only be undertaken when other causes of growth failure (e.g. hypothyroidism, chronic systemic disease, Turner syndrome, skeletal disorders) have been excluded by careful history taking, clinical examination and initial investigations. Assessment of the GH/IGF-1 axis requires GH provocation testing; random GH measurements are of little value. Measurement of serum IGF-1 or IGF-BP3 concentrations may also be helpful.

**2. Initial Clinical Assessment and Investigations**

If there is clinical concern about a child's short stature or height velocity<sup>6</sup> and the bone age is significantly delayed compared to chronological age, the following initial laboratory tests are recommended:

- a) blood samples for full blood count, glucose, U&E (sodium, potassium, urea, creatinine), calcium, phosphate, alkaline phosphatase, C-Reactive Protein, thyroid function (TSH and free T4), coeliac disease antibodies (preferably anti-TTG, with IgA measurement to exclude selective IgA deficiency) and in girls, assessment of the karyotype.
- b) urine testing for protein and glucose.

### 3. IGF-1/IGF BP3 measurements

- a) Serum IGF-1 and/or IGF-BP3 results should be interpreted against bone age using age and gender-related reference ranges.<sup>6</sup>
- b) Decreased concentrations of IGF-1 and/or IGF-BP3 strongly suggest an abnormality in the GH axis if other causes (e.g. poor nutrition, liver disease) have been excluded.<sup>6</sup>
- c) IGF-1 and IGF-BP3 results within the reference range can occur in children with GHD.<sup>6</sup>

### 4. GH Provocation testing

- a) In suspected isolated GH deficiency, two GH provocation tests are recommended.<sup>1</sup> GHD should only be diagnosed if both tests demonstrate inadequate GH responses. The tests should be performed sequentially. The second test is only required if there is an inadequate GH response in the first. Evaluation of other aspects of pituitary function should be undertaken as clinically indicated.
- b) In children with defined central nervous system pathology, history of irradiation, multiple pituitary hormone deficiency or a genetic defect affecting the GH axis, one GH provocation test will suffice.<sup>1</sup>
- c) Clonidine, arginine, glucagon or insulin are suggested provocative agents and should be used after an overnight fast in a well-standardised protocol.<sup>6</sup> Where a second GH provocation test is required, the use of a different provocative agent from that used in the first test is suggested. Insulin-induced hypoglycaemia should not be used in children aged under five years in whom the glucagon test may be more appropriate.
- d) Clonidine (0.15 mg/m<sup>2</sup>) should be given orally, with blood samples for GH measurement collected at 0, 30, 60, 90 and 120 minutes.<sup>9</sup> The patient should be monitored for possible hypotension.
- e) Arginine HCl (0.5 g/kg body weight, maximum 30 g) should be infused i.v. (10% arginine HCl in 0.9% NaCl at a constant rate over 30 minutes). Intravenous patency should be frequently assessed and there should be limited movement of the patient during the infusion. Blood samples for GH measurement of GH should be collected at -30, 0, 30, 60, 90 and 120 minutes. As a precaution an antihistamine and adrenaline should be available for treatment of potential allergic reactions to arginine. Arginine should **NOT** be used in patients with electrolyte or acid base disturbance, uraemia, diabetes or in those with renal or liver disease.
- f) **Great care should be exercised when performing insulin-induced hypoglycaemia or glucagon stimulation tests.** These tests require very careful supervision and should **ONLY** be undertaken by experienced staff working in a specialist unit where these tests are frequently undertaken. Given the risks of tests involving hypoglycaemia, it is recommended that in non-specialist units Clonidine and Arginine tests should be used to test for GHD.
- g) Sex steroid priming is not routinely recommended given the absence of a consensus on whether it is necessary.

## 5. Analytical Considerations

- a) The definition of a normal response remains arbitrary as there is a continuous spectrum of GH secretion in childhood. In a child with clinical criteria for GHD, peak GH concentrations below 20 mU/L have traditionally been used to support the diagnosis.<sup>1</sup> However, this value will vary depending on the GH immunoassay used. Clinicians and laboratories should be aware of GH assay methods in use, their limitations and cut-offs.
- b) Laboratories referring samples elsewhere should quote the same cut-off limits as the laboratory performing the assays.
- c) Each laboratory performing GH, IGF-1 and IGF-BP3 assays should be CPA accredited and should ensure that appropriate internal quality control (IQC) and external quality assessment (EQA) procedures are in place.

## 6. Further management

- a) If a diagnosis of GHD is confirmed, the case should be discussed with a specialist in paediatric endocrinology and consideration given to testing other pituitary hormones. Magnetic resonance imaging of the brain, with particular attention to the hypothalamic-pituitary region, should be carried out in any child diagnosed as having GHD, to exclude the possibility of a tumour.<sup>1</sup>
- b) Treatment with recombinant GH is recommended if GHD is confirmed.<sup>1</sup> GH treatment should, in all circumstances, be initiated and monitored by a paediatrician with special expertise in the management of children with GH disorders.<sup>1</sup> Continuation of treatment can be maintained under an agreed shared-care protocol with a general practitioner.
- c) After attaining adult height, re-testing of the GH/IGF-1 axis should be undertaken after discussion with an adult physician with expertise in endocrinology, as GHD may persist.<sup>1</sup>

## REFERENCES

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9. Gil-Ad I, Topper E, Laron Z. Oral Clonidine as a Growth Hormone stimulation test. Lancet 1979; **2**: 278-280.

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**Appendix: Calendar of Audit Process for Standards for Investigating Short Stature in Children**

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|-------------|--|
| March 2001  | Survey of Welsh laboratories' and paediatricians' strategies for investigating short stature in children (13/13 centres replied) undertaken by Dr.C.Evans (Principal Biochemist, University Hospital of Wales, Cardiff). Findings presented at an All Wales Clinical Biochemistry Audit Group meeting at the Vale of Glamorgan Hotel, Hensol on 30 <sup>th</sup> March 2001. |
| Early 2002  | Paper based on audit findings, with draft recommendations, prepared by Dr.C.Evans and Dr.J.Gregory and submitted to the Journal of Clinical Pathology. Revised version of paper accepted for publication later in 2002.  |
| Summer 2002 | Initial draft standards prepared and sent for consultation to paediatricians with an interest in endocrinology and clinical biochemists in Wales to seek their views.  |
| Nov. 2002   | Standards presented at the All Wales Clinical Welsh Biochemistry Audit Group meeting on 8 <sup>th</sup> November 2002 and considered at an All Wales Clinical Biochemistry Audit Group committee meeting on 4 <sup>th</sup> December 2002.   |
| March 2003  | Final version of standards ratified by All Wales Clinical Biochemistry Audit Group committee (chairman Dr.K.Griffiths).  |
| 2006        | Proposed date of re-audit and review of standards.   |