Growth hormone deficiency – Difficulties in Diagnosis and Management

a report by
Anitha Kumaran¹ and Mehul Dattani²

¹. Specialist Registrar, Paediatric Endocrinology, Great Ormond Street Children’s Hospital; ². Professor of Paediatric Endocrinology, Institute of Child Health, and Honorary Consultant, Great Ormond Street Children’s Hospital and University College London Hospital

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Growth hormone (GH) secreted by the pituitary gland is the principal mediator of somatic growth in childhood. Growth hormone deficiency (GHD) has an incidence of approximately one in 3,000–4000.¹² This may be an overestimate, as reversibility of GH deficiency has been reported in 25–75% of children with GHD.³ It may occur in isolation (IGHD), or in combination with other hormone deficiencies (multiple pituitary hormone deficiency [MPHD]).

Additionally, it can occur in association with other congenital abnormalities such as forebrain defects, optic nerve hypoplasia or cleft lip and palate. A threshold of height standard deviation score (SDS) equal to or below 2.0 (3rd percentile) will identify 14% of children with an organic cause of growth failure.⁴,⁵ After excluding chronic, non-endocrine causes of growth failure, these children should be assessed for GHD if there is an association of poor growth velocity (height velocity >1 SD below mean for chronological age).⁶

**Diagnosis**

The diagnosis of GHD in children has been the subject of controversy for decades. Diagnosis can be extremely difficult owing to the fallibility, lack of reproducibility and poor sensitivity and specificity of the various biochemical tests involved. Accurate height measurements with appropriate measuring devices plotted on appropriate charts by staff trained in auxology are imperative to diagnose growth failure.¹ Serial measurements over at least six months to one year are necessary for calculating height velocity.⁶

Thyroxine and cortisol are necessary for regulation of the GH gene, so normal concentrations of these hormones are necessary before testing for GH deficiency. Random GH measurements are unhelpful in diagnosing GHD due to the pulsatile nature of GH secretion. Urinary GH secretion lacks adequate sensitivity and specificity for the diagnosis of GHD.⁹

The commonly used method to diagnose GHD is growth hormone provocation testing. The National Institute for Clinical Excellence in the UK (NICE) recommends that at least two tests of GH provocation must be performed to diagnose GHD. There is at present no satisfactory solution if the two provocation tests produce conflicting results. The cut-off value to diagnose GHD is any value less than or equal to 5–6.7mcg/l (15–20mU/l). This is an arbitrary cut-off value as even normal children can have low peak GH values.¹⁰ This cut-off value may be used independently of the type of test and assay methodology involved, which makes interpretation difficult as it is well known that there is not only considerable inter- and intra-individual variation with these tests, but the cut-offs used also vary depending on the assay used.¹¹,¹² These tests are considered to be non-physiological as they are not representative of the normal secretory pattern of pituitary GH. Additionally, the tests can be associated with significant morbidity and even mortality.¹²

While provocation tests can diagnose complete GHD, the boundaries between partial GHD, idopathic short stature and constitutional delay of growth and puberty are blurred. Additionally, in children with neurosecretory dysfunction of GH secretion, the diagnosis can be missed as they have a normal GH response to stimulation but have decreased spontaneous GH secretion.⁶

The influence of age and sex steroids on GH testing is another area of debate. Although the consensus statement of the Growth Hormone Research Society⁶ does not recommend sex steroid priming prior to GH testing, it has been shown that 61% of normal pre-pubertal children failed to raise their peak GH level above 7.2ng/ml following three provocation tests.¹³ Hence, sex steroid priming is still practised despite a lack of consensus. Variation in GH concentrations is marked with the use of different GH assays in different studies.¹³,¹⁴ The assays in use detect immunologically active hGH, which may not reflect true biological activity. Immunofunctional assays (IFAs) represent an advance as they detect hGH capable of binding to its receptor. A comparison of IFAs with immunoradiometric assays demonstrates different GH concentrations within the same serum sample.¹⁵

The GH-dependent growth factors insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3) lack adequate sensitivity for the diagnosis of GHD but have a combined specificity of 90%, which would indicate GHD if values are subnormal.
and other contributing causes (nutrition, renal and hepatic dysfunction and underlying disease) are excluded. IGF-1 concentrations are highly age-dependent, with very low concentrations in early childhood and a dramatic increase in puberty. However, a combination of HV and IGF-1 concentrations has a high sensitivity (95%) and specificity (96%) in diagnosing GHD, and may replace the need for a second growth provocation test.

**Imaging**

Bone age estimated by X-ray of the left wrist and hand is a useful tool in the evaluation of all children with growth failure. Recently, the use of magnetic resonance imaging (MRI) has helped enormously in the diagnosis of GHD and related disorders. Abnormalities are associated with both IGHD and MPHD. Common abnormalities are a small anterior pituitary gland, attenuated or absent pituitary stalk and an ectopic or undescended posterior pituitary. Suspicion of intracranial tumours, infiltrative disorders and structural abnormalities should also prompt an MR of the central nervous system.

**Genetics**

Recent advances in our knowledge of the developmental processes regulating normal pituitary development have led to the identification of a number of genetic causes of GHD and hypopituitarism. For instance, mutations in the developmental gene HESX1 are associated with septo-optic dysplasia (SOD), MPHD and IGHD, while mutations in the genes SOX3, LHX3, LHX4, PROPI and POU1F1 are associated with variable forms of hypopituitarism. Mutations in the genes encoding GH and the growth-hormone-releasing hormone receptor (GHRHR) are associated with IGHD. However, variability of phenotypes and penetrance, as well as the rarity of mutations, suggests that genotyping cannot currently be used for the diagnosis of GHD. Currently, the gold standard for diagnosis is a combination of clinical, auxological, biochemical and radiological data that support GHD.

**Treatment**

The unlimited supply of recombinant human growth hormone (rhGH) introduced in 1985 has led to optimal dosing and adequate duration of treatment with a good safety profile. Children treated early have good catch-up growth and normal final adult height (FAH). The recommended dose of rhGH for use in GHD is 20–30µg/kg/day. A dose of 0.18mg/kg/week rhGH has been shown to be sufficient to reach FAH within two SDS of the normal population.

The variables that influence final height are dose of GH, duration of treatment, height SDS at the start of treatment, bone age delay, height at puberty onset, midparental height and first year of treatment growth velocity (GV), all of which showed a positive correlation; age at start of treatment and maximum GH peak in stimulation tests are negatively correlated.

Another possible factor influencing hGH responsiveness and final height is a polymorphic variant resulting in the deletion of exon 3 in the gene encoding the growth hormone receptor (GHR gene). The two main polymorphic variants in GHR result in the retention (GHRfl) or deletion of exon 3 (GHRd3). In children born small for gestational age (SGA), the GHRd3 genotype has shown increased responsiveness to GH therapy. In children with GHD and MPHD, the presence of GHRd3 genotype has generated data ranging from no influence on GH responsiveness to improved first-year growth velocity and an increase of 0.9 SDS in final height compared with GHRfl genotype. It is unclear if the dose of GH or the severity of GHD might contribute to these conflicting reports.

GHD has been shown to reverse in 25–75% of GHD patients, when re-tested after a washout period of one to three months. Recent data show that 36% of children diagnosed with isolated GHD without alterations in pituitary anatomy on MRI normalised on re-testing of their GH–IGF axis at puberty, and discontinuation of rhGH in these children did not significantly alter their final height. This could indicate the presence of a transient GH deficiency that corrects under the influence of pubertal steroids, or reflect the lack of reproducibility of the biochemical tests. This might validate earlier withdrawal of treatment, especially in children with partial GHD.

Recently, the continuation of GH treatment in adults with persisting GHD has been recommended by the National Institute for Clinical Excellence (NICE) in the UK. In adults, GHD has been associated with increased fat mass, decreased lean body mass, increased triglycerides and high-density lipoprotein contributing to cardiovascular morbidity. Reduction in bone density and exercise capacity secondary to reduced muscle mass has also been reported. It is well known that GHD has a significant impact on quality of life and is associated with reduced energy levels, concentration and emotion. NICE guidelines recommend that GH treatment should be considered only in adults who have fulfilled criteria on a quality of life questionnaire. rhGH has shown to improve body composition, lipid profile, bone density, quality of life and cardiovascular morbidity. The Growth Hormone Research Society recommends a lower dose of 0.15–0.30mg/day to minimise side effects, with subsequent optimisation of the dose based on IGF1 concentrations.

Currently, it is recommended that GH secretion should be reassessed at the end of statural growth, and GH therapy continued only in cases of severe GHD (peak GH<3mcg/l); individuals with moderate GHD (peak 3–7mcg/l) should be followed up by an adult endocrinologist.
Pituitary Disorders

There is no need for re-testing in patients with MPH, GHD due to a congenital lesion or a genetic mutation, and GHD secondary to radiotherapy, surgery or a mass lesion as it is unlikely that their GH deficiency will reverse.

Conclusion

In several fallacies and careful consideration of clinical, auxological, biochemical and radiological data is required for appropriate diagnosis. Understanding the role of growth hormone in metabolic and psychological aspects of GHD has led to better management of GHD in adulthood but long-term follow up is required to assess the impact of rGH on lifespan in GHD adults and the safety profile of prolonged treatment. With further advances in medical technology, better investigation modalities might emerge, with a consequent impact on management.