TOO LITTLE, TOO LATE – PAEDIATRIC USE OF GROWTH HORMONE THERAPY

Introduction

Growth failure in children can be associated with considerable stigma, low self-esteem, and learning and behavioural problems during childhood, and in some conditions may also increase the risk of diabetes, cardiovascular disease and osteoporosis later in life.¹

Growth failure can be due to growth hormone deficiency (GHD) - a relatively uncommon (1 in 4 000 children) and heterogeneous disorder in terms of aetiology, pathogenesis, age of diagnosis and the cause of growth retardation and short stature.² Children with untreated GHD show decreased bone mineral density, decreased lean mass and increased fat mass. Multiple studies have shown that treatment with recombinant human growth hormone (r-hGH), or somatropin, improves these abnormalities.³ Once a diagnosis of GHD has been made, it is recommended that treatment with r-hGH is initiated as soon as possible.⁴

Available data show that the importance of early life GHD diagnosis and r-hGH treatment extends beyond attaining genetic height potential, but also to minimising or preventing the development of adverse auxological, metabolic and neurodevelopmental effects.²

KEY MESSAGES

- Children with untreated GHD do not attain their genetic height potential and show decreased bone mineral density, decreased lean mass and increased fat mass
- GHD may be isolated (IGHD), part of a multiple pituitary hormone deficiency, or result from insult to the area; affecting the ability to secrete growth hormone
- Diverse tests are required to make a GHD diagnosis correctly
- Once a diagnosis of GHD has been made, it is recommended that treatment with r-hGH (somatropin) is initiated as soon as possible
- Early life treatment with somatropin restores normal growth, with the possibility of reaching genetic height potential
- Other important beneficial effects of somatropin initiation before three years of age include changes in lipid profile, increase in bone mineral density, behavioural changes and improvement in self-perception
- Long-term growth response to r-hGH treatment may be conditioned by pre-treatment and treatment related factors; most importantly genetic height potential, severity of disease at diagnosis and age at initiation of therapy
- Delays in somatropin therapy compromise adult height attained.
Growth hormone deficiency

GHD occurs when the pituitary gland does not produce enough human growth hormone (hGH). This may express as isolated GHD (IGHD) due to genetic mutation, as part of a multiple pituitary hormone deficiency (MPHD), or result from insult to the area such as tumour, surgery, and/or cranial irradiation (Table 1).1,3,5

Approximately 50% of GHD in children is idiopathic. Severe, permanent idiopathic IGHD is frequently congenital and refers to the complete or near-complete inability to secrete GH, resulting in extremely slow growth velocity and adult height (AH) many standard deviations (SD) below the mean.1,3 Congenital micropenis and/or hypoglycaemia may be the presenting symptoms in some patients, before growth is significantly impaired. Early diagnosis is required to avoid severe hypoglycaemia and rapid growth retardation.1,6 In children with idiopathic GHD, somatropin treatment restores normal growth, with the possibility of achieving AH within the mid-parental height (MPH) range; however, delays in both diagnosis and therapy compromise AH attained. Gains in final height for somatropin treated GHD compared with untreated GHD range from 8-11cm.1,3,7

Early GHD diagnosis and a concomitant early start of somatropin treatment (<3 years of age) has proven effective in normalising height,2 but also shows several other important beneficial effects including changes in lipid profile, increase in bone mineral density, behavioural changes, and improvement in self-perception. Somatropin treatment can, in addition to promoting growth, improve quality of life and may also reduce long-term risk of cardiovascular disease, diabetes and fracture.1

Diagnosis

It is important to make the GHD diagnosis correctly, using diverse tests (Table 2). Somatropin therapy is highly efficacious so a missed diagnosis will result in a poor outcome. Equally, a false positive diagnosis will lead to many years of daily subcutaneous injections, significant wasted expenditure and unnecessary exposure to potential adverse effects (Table 3).1,8

GH secretion exists in a continuum from normal through to severe GHD. The cornerstone of GHD diagnosis is that an inadequate secretion of endogenous GH must be proven or at least be made likely. The diagnosis of GHD is often very clear in a child with MPHD or where the child presents with severe IGHD. In observational studies of severe IGHD, provocation tests show GH concentrations very distinct from the normal range (typically with peak GH <3µg/L). In children diagnosed with GHD before the age of four years, brain magnetic resonance imaging (MRI) shows abnormalities in most cases, so that MRI may represent the first-line investigation for diagnosis of GHD in infancy and early childhood.8,9

GH provocation tests can lead to a substantial percentage of false-positive GHD diagnoses. There is debate over their reliability, as lack of any gold standard has led to the development of arbitrary cut-off levels.4,8,9 The Paediatric Endocrine Society (PES) strongly recommends against reliance on GH provocative test results as the sole diagnostic criterion of GHD. GH responses to provocative testing are blunted in obese or overweight individuals, and the peak values decrease with increasing body mass index (BMI). Unlike adults, obesity-dependent modifications to diagnostic criteria in children are undetermined.3
Because of GH assay variability, a GH ≤5μg/L in the first week of life in a neonate with other pituitary hormone deficiency and who experiences hypoglycaemia is likely sufficient to accurately diagnose GHD. Outside of the neonatal period, measurement of random serum GH concentrations are of no clinical value. Beyond the first week of life there is an overlap in peak GH concentrations between children with GHD and those with normal growth and, due to this lack of GH level threshold specificity, a low GH concentration at the time of hypoglycaemia is alone insufficient to diagnose GHD. Non-severe, or partial, idiopathic IGHD is diagnosed with stimulated GH levels of >7μg/L to <10μg/L.3,4,9,10

Treatment using r-hGH

PES recommends the use of weight-based or body surface area (BSA)-based r-hGH dosing in children with GHD; an initial dose of 0.16–0.24mg/kg/week (22–35μg/kg/day), with individualisation of subsequent dosing based on clinical response.3 It has become clear that there is not only a wide range of GH secretion among individuals, but a similarly wide range of sensitivity to GH, so that one standard dose (per body size) of r-hGH would not seem rational.9 Hence, dose may be increased in non-responders, or a high starting dose may be used in very short children or in children with non-severe GHD.4,11,12

Measurement of serum insulin-like growth factor-I (IGF-I) levels is used to monitor adherence and IGF-I production in response to r-hGH dose changes. If serum IGF-I levels rise above the laboratory-defined normal range for the age or pubertal stage of the patient, PES recommend that the somatropin dose should be lowered.3

Since the body of evidence is conflicting on the comparative effectiveness of different r-hGH doses on AH and considering that high dosing carries a higher risk of long-term adverse effects, PES recommends initiation of r-hGH at the lower dose range.3

Predictors of response to r-hGH treatment

Long-term growth response to r-hGH treatment in GHD children may be conditioned by both pre-treatment and treatment-related factors, such as birth weight, baseline height SD score (HtSDS), age at the onset of treatment, height at the start of puberty, treatment duration, MPH, mean frequency of injections, and doses of GH. Other variables that correlate with total height increment include first-year growth velocity, the maximum GH peak on provocative testing and presence or absence of MPHD.2,3 The highest positive correlation with HtSDS has been reported as the MPH SDS.1,7,12 Genetic height potential is a decisive factor for AH in normal children and can also affect the response to

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Table 2. Investigations for GHD

- Exclude hypothyroidism
- GH stimulation test and measurement of IGF-1±IGFBP-3 concentrations
- Pituitary MRI in all confirmed patients with GHD and those with known or suspected intracranial tumours, optic nerve hypoplasia/ septo-optic dysplasia or any other neurodevelopmental defects
- For IGHD, two independent provocation tests are required
- In those with a history of defined CNS pathology, history of irradiation or genetic defect known to cause GHD or MPHD, one provocation test is sufficient.
treatment in GHD. Children with IGHD and with short parents respond weakly to r-hGH treatment and those with a higher target HtSDS grow more than those with a lower target HtSDS; which is not surprising given that short children with tall parents have a greater genetic height potential than those with short parents.

Baseline variables that predict favourable height outcome with somatropin therapy include younger age at start of GH treatment, greater bone age delay, pre-pubertal status, and severe GHD.

Factors repeatedly indicated as critical in pre-pubertal children are age and severity of growth retardation at diagnosis.

Patients with non-severe GHD demonstrate lower near AH (NAH) SDS and lower change in HtSDS than those with severe GHD. A more pronounced increase in HtSDS to AH is seen in children with severe GHD (GH stimulation peak <3.3μg/L) who started treatment before the age of six years, than in children of the same age with partial GHD (GH stimulation peak ≥3.3μg/L) or those who started treatment at an older age.

Effect of age at r-hGH treatment initiation

Numerous studies have highlighted the benefits of early r-hGH treatment initiation in children with GHD. A short-term study, from the 1990s, of r-hGH treatment before three years of age shows marked early catch-up growth with mean height gain approximately 3SDS after four years of therapy. The rapid and almost complete return to normal height obtained by mid-childhood in this study supports the need for r-hGH treatment in early diagnosed GHD children.

More recent studies, such as the NordiNet International Outcome Study (IOS), have provided further evidence for earlier r-hGH treatment initiation. NordiNet IOS is a non-interventional, multicentre study evaluating the long-term effectiveness and safety of somatropin as prescribed by treating physicians in the real-life clinical setting. Among other variables, the effect of age at r-hGH treatment start on NAH SDS was assessed. The enrolled children (n=172) treated to NAH (height at ≥18 years; or height velocity <2cm/year at ≥16 years for boys, or ≥15 years for girls) were grouped by age at treatment start - early (girls <8; boys <9 years), intermediate (girls 8–10; boys 9–11 years) or late (girls >10; boys >11 years) - and GHD severity (<3ng/mL or 3-≤10ng/mL).

Age at treatment start had a marked effect on NAH SDS, that achieved by patients starting treatment early (least squares mean (standard error): −0.76 (0.14)) exceeded that achieved by those starting later (intermediate: −1.14 (0.15); late: −1.21 (0.10)). Multiple regression analysis showed a significant association between NAH SDS and age at treatment start (P<0.0242). Most patients (78.5%) achieved a NAH SDS within the normal range irrespective of age at treatment start.

As expected, due to the earlier initiation of GH treatment, the mean duration of treatment to NAH was significantly longer for patients starting treatment at a young age (P<0.0001 for early vs both intermediate and late groups). The lower NAH SDS in late treatment may reflect the significantly shorter duration of pre-pubertal treatment, despite older age at pubertal onset. Aside from the evidence that age at treatment start is inversely associated with the response to therapy, starting GH replacement early also allows a longer duration of treatment and therefore more time for catch-up growth before children reach puberty, with the potential for better outcomes.

Data from the American Norditropin® Studies: Web-Enabled Research (ANSWER) Program were analysed for NAH from age at treatment start (girls <10 vs ≥10 years; boys <11 vs ≥11 years). Showing significantly greater changes in HtSDS during both years 1 and 2 of treatment, negative correlations indicate that an earlier age at treatment start would likely have resulted in greater gains in height achieved in both male and female patients.

The Genentech National Cooperative Growth Study of r-hGH treatment in children younger than two years, consequently followed up to NAH, report that a normal pattern of linear growth was achieved during childhood (<10 years) and that no additional gain in NAH SDS was realised during puberty. This is consistent with evidence that sensitivity to GH is greater during childhood and that
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Therapeutic efforts to maximise height should be concentrated in the pre-pubertal years. The strong correlation between the prepubertal height increment and total height gain is further supported by the Pfizer International Growth Database (KIGS). Assessment of NAH in 1,258 r-hGH treated patients with IGHD or MPHD showed that although pubertal growth accounts for 20–35 cm of the height gain, it is clear that the most successful strategies for enhancing r-hGH-induced growth must concentrate on growth during early childhood rather than attempt to modulate the pubertal growth process. Retrospective analysis of clinic data showed superior HtSDS in pre-pubertal treatment initiation; however the height gain obtained during puberty was higher in patients starting r-hGH treatment during the pubertal period.

In summary, most r-hGH treated patients with IGHD (89%) and MPHD (81%) achieve NAH within their genetic potential, with most of the height gain associated with pre-pubertal therapy. Early treatment start is associated with improved AH outcomes.

Psychological, neurodevelopmental and metabolic outcomes

Recent studies have conclusively shown that GH and IGF-I receptors are located throughout the brain, particularly in regions related to learning and memory, and a large amount of data suggest that GHD and reduced IGF-I levels may correlate with decreased cognitive ability. Infants and toddlers treated with r-hGH seem to be more alert and energetic, as reported by their families; and an increased rate of language and cognitive development was reported, even if such results may only be due to increased muscle tone. Children with IGHD have improved intellectual development if they are treated before the age of five years and present with improved attention, anxiety, social competence, and thought impairment after three years of treatment.

Data on lipid profiles in children with untreated GHD compared to healthy controls and the effect of r-hGH treatment thereon are inconsistent. It remains to be established if there is long-term protection for those with high cardiovascular risk receiving r-hGH therapy.

Conclusions

Important factors for reaching AH within the normal range are early diagnosis, patient compliance, daily injections and ensuring the best SDS possible until the start of puberty. The time available to maximise growth is limited in pubertal cases, and early initiation of GH treatment in children with isolated GHD improves their chance of achieving their genetic height potential. Early and aggressive diagnosis and treatment of GHD are the most likely ways to achieve successful height outcomes in the most economically prudent fashion. Additionally, the psychological benefits are greater, and metabolic and neurodevelopmental benefits may be seen in childhood and adulthood.

Despite the multiple benefits of early initiation of r-hGH therapy for GHD, many patients still start treatment late (girls >10 years, boys >11 years), which may compromise their chances of achieving their genetic height potential. In general, more boys than girls with GHD are treated, so it is important to avoid delayed or missed diagnoses in girls.

References


