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Chairman's Summary: Diagnostic Techniques for Identifying Children with Idiopathic Short Stature

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Idiopathic short stature (ISS) is a diagnosis that includes an extremely heterogeneous group of children, ranging from those with normal variants of growth, such as familial short stature and constitutional delay of growth and puberty, to those with rare molecular alterations that affect the function of the growth hormone–insulin-like growth factor I (GH–IGF-I) axis. The clinical implication of this heterogeneity is that the individual response to GH and/or IGF-I therapy depends largely on the mechanism underlying ISS. Identification of the molecular defects that can result in growth retardation is often difficult, if not impossible. The availability of criteria for identifying potential responders would permit the selection of patients who will benefit from such interventions, thus avoiding lengthy, expensive, useless or potentially harmful therapies in patients with a small likelihood of response.

In this section, the authors examine the predictive value of auxological and laboratory criteria to determine which patients would respond to GH–IGF-I therapy with increased adult height. Unfortunately, the available evidence indicates that there is not a single parameter, but rather a constellation of parameters that drive the decision for treatment on an individual basis. Currently, no single auxological or biochemical measure is accurate enough to dictate the therapeutic choice. Further studies are required to better characterize the different conditions underlying ISS.

Disclosure Statement

S.C. serves on advisory committees/review panels for Pfizer.

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Auxological Criteria for Treating Children with Idiopathic Short Stature

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Key Words

Auxological criteria · Growth hormone treatment

Abstract

Children with idiopathic short stature (ISS) may not reach an adult height within their genetic target. In 2003, the United States Food and Drug Administration approved biosynthetic growth hormone (GH) for the treatment of children with ISS whose heights exceeded 2.25 standard deviation scores below the mean and who were considered unlikely to reach a normal adult height. Results of controlled studies have shown that, although GH treatment leads to a substantial increase in adult height, the individual response to therapy is difficult to predict. A number of auxological variables (i.e., age and height at start of treatment, bone age delay, mean predicted height, height velocity and first-year responsiveness) are used in multivariate analyses to predict outcomes. Estimation of target height, predicted adult height and pattern of growth should guide the decision to treat a child with ISS.

Introduction

Children with idiopathic short stature (ISS) often fail to reach an adult height (AH) within their genetic target, a prediction based on parental height [1]. This consideration prompted the use of growth hormone (GH) treatment in children with ISS with the specific aim of increasing growth velocity and adult height. Numerous studies (reviewed by Wit et al. [2]) have shown that a short-term course of GH (e.g., 6 to 12 months) increases growth velocity in the majority of children. Long-term data on AH, however, show a wide interindividual variability of response. In 2003, the United States Food and Drug Administration (FDA) approved biosynthetic GH for the treatment of children with ISS whose heights exceed 2.25 standard deviations (SD) below the mean and who were considered unlikely to reach a normal AH. Readily available information regarding the auxological criteria for treating children with ISS with GH is summarized.

Which Auxological Criteria Are Useful to Predict AH in Children with ISS?

Height

Although the FDA approved GH treatment for children with a height standard deviation score (SDS) below –2.25, an international consensus formed at a meeting on the Diagnosis and Treatment of Idiopathic Short Stature [3] considered GH therapy appropriate in children whose heights ranged between –2 and –3 SDS below the mean. For children younger than 5 years, height should be plotted using the recently published growth charts by the World Health Organization [4]. For older children, ethnic-specific growth charts are preferred.

Target Height

Target height (TH) reflects the genetic height potential inherited from parents, and the TH range is defined as approximately 1.6 SD around the TH [3]. The height of children with familial short stature (FSS) is within the expected TH range, while that of children with nonfamilial short stature (NFSS) is below the expected TH range. On average, the AH of children with ISS is below the TH [1, 5]. Several methods exist for estimation of TH, and the proportion of children with FSS or NFSS varies depending on the method used [6]. The method of choice according to the Consensus Conference is the following algorithm: 0.72 × the average of the father's and mother's height SDS. The lower limit of the TH range was calculated as TH –1.6 SDS [3].

Predicted Adult Height

Predicted adult height (PAH) is estimated based on assessment of bone age and is validated in children with normal height and weight. In children with ISS, there is generally a good correlation between PAH and AH; however, on an individual basis, PAH is inaccurate. In patients with delayed bone age, PAH is often overestimated [1, 7].

Growth Velocity

A child whose growth velocity was persistently below the mean would be expected to reach an AH below the mean, provided he/she did not experience catch-up growth at puberty. Children with ISS and pubertal delay who show a persistently low growth velocity and a progressive reduction of relative height may not reach their TH [8].

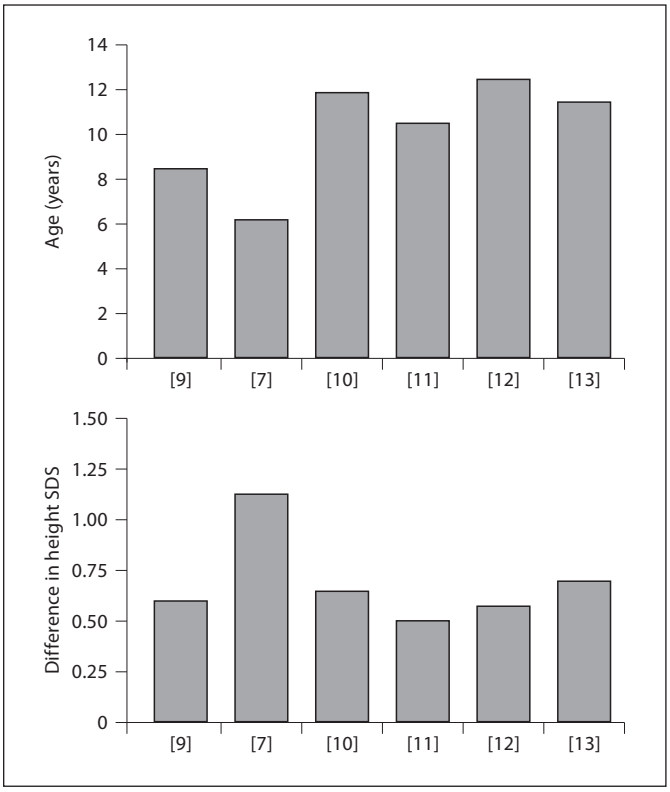

Fig. 1. Mean difference in height SDS (lower panel) based on mean age at start of treatment (upper panel) between children with ISS treated with GH and control subjects. Numbers in brackets denote the studies [as numbered in the Reference list] from which the data were derived.

Which Auxological Criteria Are Useful to Predict the Response to GH Treatment?

More than 20 studies have reported data on AH or near-AH in children with ISS [2]. However, only six of these 20 studies were controlled [7, 9–13]; three of these were randomized [10, 12, 13] and one was placebo-controlled [12]. These studies have shown that GH treatment increases AH in children with ISS, but the results are highly variable ranging from no difference compared with a control group to an increase of 2 SDS. Patients with NFSS were found to respond better than those with FSS [7, 13]. Multivariate analyses have been used to identify auxological predictors of outcomes. Leschek et al. developed a prediction model that explained 84% of the variation in height gain [12]. Albertsson-Wikland et al. found that 58% of the variation in AH SDS was due to the GH dose, height SDS at baseline, bone age delay, insulin-like growth factor I SDS and differences in mean predicted height (MPH) both at birth and at baseline [13]. Analysis of the Pfizer International Growth Study Database (KIGS) showed that AH correlated positively with baseline height, MPH and the first-year responsiveness to GH treatment, and negatively with age at the start of GH treatment [14]. Interestingly, a comparison of the efficacy of GH treatment reported in the different studies revealed that the best results were obtained in patients who began treatment at an earlier age (fig. 1).

Conclusions

Children with NFSS, younger age at presentation, reduced height velocity and low PAH may not reach a normal AH. Treatment with GH improves AH, but the individual response is unpredictable. Results from available studies indicate that AH after GH treatment is influenced by age and height at start of treatment, bone age delay, MPH, height velocity and response during the first year of therapy. Further studies are needed to more precisely identify children who may truly benefit from GH treatment.

Disclosure Statement

S.L. is a speaker/teacher for Pfizer, Serono, Lilly and Ipsen, serves on advisory committees/review panels for Serono and Pfizer and is an investigator in clinical trials sponsored by Serono, Ipsen and Lilly.

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Criteria for Treating Children with Idiopathic Short Stature: Laboratory (Biochemical)

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Key Words

Idiopathic short stature · GH-IGF axis · Treatment · Laboratory test · IGF-I

Abstract

Idiopathic short stature (ISS) is a diagnosis of exclusion. No specific laboratory test can identify it. Rather, a series of tests that examine a person's genetic, nutritional and hormonal makeup are used to exclude specific diagnoses. However, abnormalities of the growth hormone-insulin-like growth factor (GH-IGF) axis appear to be common in children with ISS. As the only growth-promoting treatments available to children with ISS are either human GH or recombinant human IGF-I, it is plausible that measures of the GH-IGF axis or of growth factor response might be useful in predicting response to therapy or choosing the optimal medical regimen.

Biochemical Tests to Diagnose Idiopathic Short Stature and Predict Treatment Response

There are several potential explanations for the growth deficit in patients with idiopathic short stature (ISS). These are: (1) subtle defects in growth hormone (GH) secretion; (2) a disturbance in GH action; (3) reduced insulin-like growth factor I (IGF-I) secretion in the face of otherwise normal GH action; (4) IGF resistance; or (5) defects in basic cell growth regulatory processes (e.g., cell cycle defects). Multiple studies have shown that circulating concentrations of IGF-I are reduced in children with ISS, with nearly all of them having levels below average for age and sex [1]. Their mean levels are somewhere between those of normal children and