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Review

Idiopathic short stature: Definition, epidemiology, and diagnostic evaluation

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Abstract

Idiopathic short stature is a condition in which the height of the individual is more than 2 SD below the corresponding mean height for a given age, sex and population, in whom no identifiable disorder is present. It can be subcategorized into familial and non-familial ISS, and according to pubertal delay. It should be differentiated from dysmorphic syndromes, skeletal dysplasias, short stature secondary to a small birth size (small for gestational age, SGA), and systemic and endocrine diseases. ISS is the diagnostic group that remains after excluding known conditions in short children.

Keywords: Growth; Short stature; Idiopathic short stature; Diagnosis; Growth hormone deficiency

1. Introduction

This is the first of a set of two review papers that provided the basis for an international consensus meeting on idiopathic short stature (ISS) held from 17 to 20 October, 2007 in Santa Monica (CA, USA). In part A, the definition and epidemiology are described; the second (part B) presents the diagnostic evaluation of the short child. The structure of these reviews is based on the questions that were posed to the participants of the meeting. In the second review [1], the management of ISS is discussed, including growth hormone treatment. The consensus statement is published separately [2].

2. Definition and epidemiology

2.1. How should ISS be defined?

In most diagnostic classifications of short stature, three main groups are distinguished: primary growth disorders (conditions intrinsic to the growth plate), secondary growth disorders (conditions that change growth plate physiology), and a remaining group in which no recognizable cause is found. This last group is currently known as ISS [3,4]. However, in pediatric practice, a wide variety of other terms are still used, including constitutional short stature, normal-variant short stature, familial short stature (FSS), small/delay, constitutional delay of growth and adolescence and familial slow maturation, defined in various ways [3].

It is generally assumed that growth is regulated by a multitude of genetic and epigenetic mechanisms

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interacting with influences from the internal and external environments. With respect to genes, it is assumed that both adult height and the tempo of growth are largely genetically programmed. Thus growth in childhood may be considered as the result of hypothetical "height genes" and "tempo genes". Both sets probably include several hundreds of genes, of which presently only a few are known [5]. Thus, in a child with a height below −2 SDS (standard deviation score) (equivalent to the 2.3rd percentile) in whom no other abnormalities can be found, there is usually a mixture of shortness-inducing "height genes" and slow maturation-inducing "tempo genes". One would expect that in short children with normal "tempo genes" adult height SDS is close to prepubertal height SDS, while in children with slow maturation-inducing "tempo genes" adult height SDS will be greater than prepubertal height SDS.

Assuming that multiple genes are involved, height in the population should have an approximately Gaussian distribution. In fact, height distribution for age is almost perfectly Gaussian in large-scale growth studies, although the numbers of individuals measured are insufficient to accurately determine the extreme percentiles. Theoretically, one would expect that the left tail of the distribution may be slightly more skewed than the right-hand tail, as height can more easily be severely inhibited than strongly increased. Individuals with a height shorter than the −2.0 SD cut-off limit of the population can either be considered as the necessary 2.3% shortest part of the "normal" distribution, or as individuals with a disorder that restricts growth.

According to an expert workshop [3], ISS is defined as a condition in which the height of the individual is more than 2 SD below the corresponding mean height for a given age, sex and population group, and in whom no identifiable disorder is present. This definition was confirmed by a recent Cochrane review [4] and the ESPE Classification of Paediatric Endocrine Diagnoses [6]. ISS is a descriptive term and can only be used if a child is short for the population to which he or she belongs and if a thorough history, physical examination and additional investigations have not identified a definite cause. More specifically, children should be considered GH sufficient, have no history of a low birth size (small for gestational age, SGA), have normal body proportions, good caloric intake and no psychiatric disorder [7].

ISS is a diagnosis that is not based on positive findings in the diagnostic workup, but on exclusion of other recognizable conditions. The ability to find underlying pathology depends totally on the completeness of the medical history, the thoroughness of the physical examination, and the choices made with respect to additional investigations. Therefore, the cornerstones of the definition of ISS are the definition of shortness, the description of the disorders that must be excluded, and the investigations necessary to make such a determination.

In terms of the cut-off limit that separates "short" from "not short", the consensus statement is clear. Short is defined as: "2 SD below the corresponding mean height for a given age, sex and population group" [3] and this cut-off has also been used in most clinical trials [4]. Thus, short stature is "abnormal" from a purely statistical point of view, which does not automatically imply that it is abnormal in the sense of a pathological condition. Although this cut-off is generally accepted for clinical purposes, it should be noted that in the context of growth hormone (GH) therapy, lower cut-off limits are being used in selecting patients for treatment, such as 2.25 or 2.5 SD below the mean in children with ISS or with persistent short stature, who were born small for gestational age (SGA).

The question of which population should be used for comparison is more difficult to answer. Basically, there are four points of contention. First, which reference population should be used if no recent large, nationwide population study is available? Second, how should a secular trend be corrected for? Third, which references should be used for children belonging to ethnic minorities? Fourth, should references be based on samples from the whole population, or only from "healthy" children?

The height of a population is influenced by (1) genetic factors associated with ethnic origin; and (2) environmental factors, of which socioeconomic conditions are the most influential. In the last 150 years, a secular trend toward increased height has been observed in Western countries. For example, in the Netherlands the secular trend is presently close to 4.5 cm per generation (30 years) [8]. A height increase of similar magnitude (1–1.5 cm/decade) is present in virtually all industrialized countries with the exception of the Scandinavian countries, where socioeconomic circumstances appear to have been favourable for so long that height seems to be close to optimal for ethnic origin and environmental conditions [9]. It has generally been assumed that this positive trend is primarily a result of better environmental conditions (more and better food, particularly protein, and fewer infections). However, part of the trend may be associated with differences in the procreative success of tall and short individuals [10]. In the US, it is uncertain if there is a secular trend, and a recent study showed that obese individuals may not reach their "ideal" height, perhaps related to slightly earlier puberty [11].

Growth charts primarily serve as a tool for screening (e.g. detecting growth disorders) and for follow-up (e.g. determining whether the individual growth curve follows the expected pattern). In most countries, the population used for reference originates either from other countries or from their own population, but collected several decades previously. Ideally, in these countries the growth references should be updated at regular