Definition and prevalence of familial short stature

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Research

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Abstract

Objective

A significant portion of familial short stature (FSS) cases may not be recognized in clinical practice if the parents’ height is not adequately investigated. This study aimed to verify the prevalence of different definition of FSS on a cross-sectional cohort of children referred for short stature (SS) when their height and that of both parents were measured.

Methods

We consecutively enrolled 65 individuals referred for SS when both parents were present. We defined “target height related short stature” (TH-SS) when child height SDS was ≤-2 and included in the range of TH (i.e. TH SDS ± 1.5) and “autosomal dominant short stature” (AD-SS) when child and at least one parent heights were ≤-2 SDS.

Results

On 65 children referred for SS, 48 individuals had a height ≤-2 SDS. Based on measured parents’ heights, 24 children had TH-SS and 16 children AD-SS; 12 children were identified by both TH-SS and AD-SS, while 12 children with TH-SS did not have any of parents with SS. When considering reported parents’ heights, 3 out of 24 children with TH-FSS and 9 out of 16 with AD-FSS would have been missed.

Conclusion

This study underlines that adequate measurement and consideration of both parents’ height should be part of the clinical evaluation of every children with SS and new definitions should be used to detect and adequately approach the cases of FSS, since the identification of a causative gene in AD-SS can support treatment and follow-up decisions.

Introduction

Short stature (SS) – defined as a height ≤-2 standard deviation score (SDS) – is the most common referral reason in pediatric endocrinology. ¹

In 23–37% of the cases, these children have a family history of SS and attain a final adult height that, despite being ≤-2 SDS, is consistent with their target height (TH): this condition is addressed as familial short stature (FSS) and has long been considered a normal variant of growth and is usually not investigated nor treated²⁻³.
However, genetic analysis's rapid progress and innovation enabled scientists to identify different monogenic gene defects causing SS, mainly with an autosomal-dominant inheritance, that may be not classified as FSS according to this definition when parents have a large difference between their height SDS. For this reason, some Authors believe that is more appropriate to consider FSS when at least one parent has height of \( \leq -2 \) SDS.\(^4\)–\(^6\)

Furthermore, a significant portion of FSS cases may not be recognized in clinical practice if the parents’ height is not adequately investigated. Family history may not be enough to identify all children having a parent with SS if we consider that parents – especially those of children referred for short stature – tend to overestimate their height.\(^7\)–\(^11\)

This study aimed to verify the prevalence of different definitions of FSS on a cross-sectional cohort of children referred for SS when their height and that of both parents were measured.

**Material And Methods**

We consecutively enrolled 65 individuals referred for SS to the Endocrine Unit of the Institute for Maternal and Child Health "Burlo Garofolo" when both parents were present. After explaining that an accurate estimate of their height was required for their children's evaluation, parents’ self-reported height was recorded (reported parent height, R-PHT). Parents and children were then measured (measured parent height, M-PHT, and child height, CHT, respectively) using a Harpenden stadiometer.

TH was calculated with the formula: \((\text{paternal height} + \text{maternal height})/2 - 6\) for females and \(+ 6\) for males using Growth Calculator 3 Software, as well as SDS for heights and TH according to Italian reference charts (Cacciari 2006).

We used the following definition for FSS:

- “target height related short stature” (TH-SS) when CHT SDS was \( \leq -2 \) and included in the range of TH (i.e. TH SDS \( \pm 1.5\));
- “autosomal dominant short stature” (AD-SS) when CHT and at least one PHt were \( \leq -2 \) SDS.

The prefixes R- and M- were added with reference to R-PHT or M-PHT, according to data used in the calculation.

The study was approved by the Institutional Review Committee (RC 33/18 Line 2).

Data were presented as percentages, median and interquartile ranges (IQRs). Mann-Whitney rank-sum tests and Two-tailed Fisher exact tests were performed to evaluate the relations between variables. A p-value \(< 0.05\) was considered statistically significant. Statistical analysis was conducted using JMP™ software (version 15.1.0, SAS Institute Inc.).
Results

Over 65 children referred for SS, 48 individuals (20 females) had a height ≤ -2 SDS (median children height SDS − 2.4 [IQR − 2.8; -2.1], median age 9.1 years [IQR 6.2; 12.4]), while 17 children (7 females) were not short (median children height SDS − 1.9 [IQR − 1.9; -1.8], median age 12.1 years [IQR 5.4; 14.3]).

When considering M-PHt, 24 children had TH-SS and 16 children AD-SS (Fig. 1). Overall 28 children were included in at least one of the two definition: 12 children were identified by both TH-SS and AD-SS, while 12 children with TH-SS did not have any of parents with SS (Fig. 2).

Children with TH-SS were significantly higher (median CHt SDS − 2.26 [IQR − 2.53; -2.15]) than other children with SS (median CHt SDS − 2.55 [IQR − 3.00; -2.31]) (p < 0.01), while children with AD-SS were shorter (median CHt SDS − 2.54 [IQR − 3.32; -2.17]) than other children with SS (median CHt − 2.44 [IQR − 2.67; -2.2]), with no statistical significance (p = 0.27).

When considering R-PHt, 3 out of 24 children with TH-FSS and 9 out of 16 with AD-FSS would have been missed (Fig. 1).

Discussion

In this study we verified that the prevalence of FSS among short children may vary according to the definition: only a third had at least one parent had a height ≤ -2 SDS (AD-SS), while half had a height consistent with TH (TH-SS) and a quarter had TH-SS without short parents. Moreover, we found that a relevant quote of FSS may be missed if clinicians only rely on reported parents’ height (56% of AD-SS and 13% of TH-SS).

Although this study refer to a small cohort in a single centre, it points the attention on the definition of FSS for its following management. We believe that the real FSS, intended as a normal variant of growth, with no need of specific investigation, should be defined as a TH-SS only when none of the parents’ heights is ≤ -2 SDS (25% of children with SS in this cohort). However, in half of TH-SS, a parent with short stature was present and, as in all cases of AD-SS (33% of children with SS in this cohort), a genetic evaluation should be required, in order to possibly investigate genetic mutation causing SS with an autosomal-dominant inheritance. In practical terms, a cut-off height for the definition of SS in parents can be identified, reducing the need for additional calculations during the medical evaluation (for instance, in the Italian population, -2 SDS height in adults corresponds to 150.9 cm for women and 164.1 cm for men).

Cases of AD-SS should not be missed, since the identification of a causative gene can support treatment decisions, allowing for a more accurate prediction of the specific response to growth hormone treatment, evaluating the recurrence risk in the family, and enabling the recognition of other features in case of a syndrome. 12
In conclusion, this study underlines that adequate measurement and consideration of both parents’ height should be part of the clinical evaluation of every children with SS and new definitions should be used to adequately detect and approach the cases of FSS, giving a concrete chance to characterize better and treat their condition.

**Abbreviations**

| Abbreviation | Definition                                      |
|--------------|-------------------------------------------------|
| AD-SS        | autosomal dominant short stature                |
| CHt          | child height                                    |
| FSS          | familial short stature                          |
| IQR          | interquartile range                             |
| M-           | measured                                        |
| PHt          | parent height                                   |
| R-           | reported                                        |
| SDS          | standard deviation score                        |
| SS           | short stature                                   |
| TH           | target height                                   |
| TH-SS        | target height related short stature             |

**Declarations**

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**Availability of data and materials**

The data that support the findings of this study are available from the corresponding author, GT, upon reasonable request.

**Ethics approval and consent to participate**
The study was approved by the Institutional Review Committee (RC 33/18 Line 2). Informed consent was provided by patients’ parents.

**Consent for publication**

Not needed.

**Competing interests**

The authors have no conflicts of interest to report and no financial interests to disclose.

**Authors’ contributions**

VG and AAO concepted the work, helped in the acquisition of data and wrote the first draft; MCP, FS and EB have drafted the work and substantively revised it; GT concepted the work, performed the analysis have drafted the work and substantively revised it. All authors have approved the submitted version.

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**Figures**

Figure 1

Distribution of children referred for short stature (SS); those with actual SS (height ≤-2 SDS); children with familial short stature (FSS) based on definition (TH-FSS, target height related familial short stature, when child height was ≤-2 and included in the range of TH (i.e. TH SDS ± 1.5); AD-FSS, autosomal dominant familial short stature, when child height and at least one parent's height were <2 SDS) and on source of parents’ height data (R for referred, in grey; M for measured, in black).
Figure 2

Distribution of children with target height related familial short stature (TH-FSS, n=24) and autosomal dominant familial short stature (AD-FSS, n=16), based on measured parents’ heights (M-). Familial short stature (FSS, n=12) is defined as TH-SS without any short parent.