

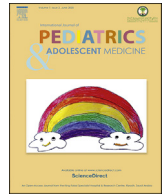
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Original article

Characteristics and etiologies of short stature in children: Experience of an endocrine clinic in a Tunisian tertiary care hospital

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ABSTRACT

Background: Short stature is a common reason for referral to pediatric endocrinology clinics. It may be a manifestation of a pathological condition requiring early treatment. The aim of this study was to describe the characteristics and etiologies of short stature among children referred to the pediatric endocrinology clinic of the main pediatric tertiary care center in Tunisia.**Methods:** Retrospective and descriptive study in the endocrinology unit of children referred for short stature between January 2012 and December 2016. Data on the patients' medical history, physical findings, laboratory tests, bone age and chromosomal analysis were collected.**Results:** 470 children (266 males and 204 females) were referred during that period. 214 (45.5%) had normal height, and 80.8% of them were referred by general practitioners. The other 256 children (54.5%) had a confirmed short stature (mean age :7.2 years, mean height: -2.77 SDS). Endocrinological causes were the most common (43% GHD, 4% hypothyroidism) followed by intrauterine growth retardation IUGR (24%), genetic syndromes (8.4%), chronic pediatric diseases (7.8%), skeletal dysplasia (6.2%), normal variant of short stature (5%), and psychosocial deprivation (1.2%). Among non-endocrine causes, Turner syndrome was the most common genetic syndrome (4.4%), achondroplasia the main skeletal dysplasia (4%) and celiac disease the main chronic disease (3.4%).**Conclusions:** ST is largely overestimated in our country. Therefore, it is important to insist on adequate measurement and analysis of growth parameters to avoid unnecessary investigations. GHD and IUGR were the most common causes. Celiac disease, though frequent in Tunisia, is not a common cause of short stature.© 2019 Publishing services provided by Elsevier B.V. on behalf of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Growth is a complex biologic process resulting from the interaction of various genetic, hormonal, nutritional, and psychosocial factors [1]. Short stature (ST) may be the expression of resulting from a disturbance in any of these factors [2]. It is growth alteration one of the most common reasons for referral to pediatric endocrinology clinics [3]. It is defined as a height below the third percentile or less than two standard deviations (SDS) below the mean for the

children of the same age, sex, and race [4].

Short stature is commonly related to a normal variant of growth, including familial ST and constitutional growth delay [5–8]. However, it may be the first manifestation of an underlying pathological condition requiring early adequate treatment, such as hormonal disorders or chronic diseases. Thus, careful evaluation and identification of the underlying etiologies is crucial for early prevention and treatment.

In Tunisia, there are no pediatric studies focusing on ST, apart from a handful of reports studying separately some etiologies of ST in children [9]. The aim of our study was to describe the characteristics and determine the etiological profile of Tunisian children referred to our pediatric endocrinology clinic for ST.

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2. Methods

This was a retrospective and descriptive study conducted in an endocrinology clinic from the center of Tunis, the one of the **major** whole university pediatric centers ($n = 13$), particularly specialized in endocrinology in Tunisia ($n = 4$) and located in the capital Tunis.

Because of its reputation, it receives patients from all regions of the country.

All new patients of Tunisian origin referred for evaluation of ST between January 2012 and December 2016 were reviewed. ST was defined as a height less than 2 SDS below the mean for the corresponding age and sex in Sempé and Pedron growth charts [10].

Eligibility requirements were as follows: (1) Children addressed for ST as the chief complaint, 2) age below 18 years, 3) adequate follow-up (for at least 6 months).

The exclusion criteria were as follows: (1) Children from non-Tunisian origin, 2) children on regular follow-up for a known and documented chronic disease or debilitating disease, or (3) children with ST but who were referred for reasons other than ST.

All patients were examined solely by two pediatric endocrinologists.

We collected data on the patients' medical history, including sex, age at diagnosis, birth weight, past medical history, nutritional history, psychosocial condition, and mid-parental height (MPH), and we specified the patient's physical findings including anthropometric measures at diagnosis (weight, height, and body mass index (BMI)), growth velocity, pubertal status, and any abnormal findings.

For the anthropometric profile of the patients and their parents, height was measured in centimeters by a standard technique using a stadiometer and weight in kilograms using a balance scale. Standing height of the patients was measured using a Harpenden fixed stadiometer (Holtain Ltd, Crosswell, UK) with a sensitivity of 0.1 cm, and body weight was measured using a balance scale (SECA, Hamburg, Germany) with a sensitivity of 0.1 kg. The weight of each child was measured with all the clothing removed except undergarment.

Target height was calculated by the method of MPH, the average of the mother's and father's height ± 6.5 cm (addition in boys or subtraction in girls).

Initial investigations performed in all our patients included complete blood count, renal function tests, free T4, thyroid-stimulating hormone (TSH), transglutaminase antibodies, and bone age. Karyotype was performed in all girls with ST in whom other causes of ST were excluded. Skeletal survey was performed when dysplasia was suspected. When growth hormone deficiency (GHD) was suspected, two stimulation tests were performed (insulin tolerance test and betaxolol-glucagon test), and the diagnosis was confirmed when peak growth hormone (GH) concentration failed to reach 10 ng/mL (20 mUI/L) [11].

2.1. Statistical analysis

Data were analyzed using the SPSS 19.0 statistical software package. Continuous data were expressed as mean \pm SD and categorical data in percentage. Comparisons were performed using Fisher's exact test for categorical variables and Kruskal–Wallis test for continuous variables. A P value < 0.05 defined the level of statistical significance.

3. Results

During the period under review, a total of 470 children (266 males and 204 females) were referred to our pediatric endocrinology clinic for ST. They were referred by general practitioners

($n = 287$, 61%), pediatricians ($n = 113$, 24%), other specialists ($n = 47$, 10%), and other healthcare professionals ($n = 23$, 5%). Among these children, 214 (45.5%) had normal height, and 173 of them (80.8%) were referred by general practitioners. The other 256 children (54.5%) had a confirmed ST. Their mean age at first evaluation was 7.2 ± 4.3 years [range: 0.5–17.5 years]. One hundred thirty-four were male (50.7%). Fifteen patients had a family history of ST (5.8%). Mean height was 105.5 ± 26.1 cm [range: 51–161 cm], which was 2.77 ± 0.92 SDS below the mean. The average MPH was 164 ± 8.18 cm [range: 142.5–188 cm]. Mean bone age delay was 1.6 ± 1.5 years [range: 0–6.5 years]. An etiology of ST was established in 179 patients (69.9%). The remaining patients were lost to follow-up before the final diagnosis ($n = 77$, 30.1%). As shown in Table 1, the most common cause of ST in our patients was endocrine disorders ($n = 85$, 47.5%), followed by intrauterine growth retardation (IUGR) ($n = 43$, 24%), genetic syndromes ($n = 15$, 8.4%), chronic pediatric diseases ($n = 14$, 7.8%), skeletal dysplasia ($n = 11$, 6.2%), normal variant of ST ($n = 9$, 5%), and psychosocial deprivation ($n = 2$, 1.2%).

The most common endocrinological etiology of ST was GHD ($n = 77$), which accounted for 43% of all etiologies and 90.6% of endocrine disorders in our study, followed by hypothyroidism ($n = 7$, 4% of all etiologies, 8.2% of endocrine disorders).

As shown in Table 2, GHD was significantly more frequent in boys than in girls ($p = 0.02$), with a sex ratio of 1.96. Two patients with GHD had evidence of other pituitary hormone deficiency.

Twenty-four (31.2%) patients with GHD had morphological abnormalities in the brain as observed by MRI, including mainly anterior pituitary dysplasia ($n = 11$), followed by pituitary stalk interruption ($n = 7$), ectopic posterior pituitary ($n = 2$), Rathke's cleft cyst ($n = 1$), Arnold–Chiari malformation ($n = 1$), sellar regional arachnoid cyst ($n = 1$), and pituitary microadenoma ($n = 1$).

Among nonendocrine causes of ST in our study, Turner syndrome was the most common genetic syndrome ($n = 8$, 4.4%), achondroplasia was the main skeletal dysplasia ($n = 7$, 4%), and

Table 1

Frequency of various etiologies among 179 Tunisian children correctly referred with short stature.

Etiology	Total n (%)	Male n (%)	Female n (%)
Normal variant of short stature	9 (5)	6 (3.4)	3 (1.6)
FSS	4 (2.2)	1 (0.6)	3 (1.6)
CDGP	5 (2.8)	5 (2.8)	0
IUGR	43 (24)	21 (11.7)	22 (12.3)
Endocrine disorders	85 (47.5)	54 (30.2)	31 (17.3)
Growth hormone deficiency	77 (43)	51 (28.5)	26 (14.5)
Hypothyroidism	7 (4)	2 (1.2)	5 (2.8)
Uncontrolled T1D	1 (0.6)	1 (0.6)	0
Dysmorphic syndromes	15 (8.4)	5 (2.8)	10 (5.6)
Turner syndrome	8 (4.4)	0	8 (4.4)
Russel–Silver syndrome	3 (1.6)	3 (1.6)	0
Other	4 (2.2)	1 (0.6)	3 (1.6)
Skeletal dysplasia	11 (6.2)	7 (4)	4 (2.2)
Achondroplasia	7 (4)	4 (2.2)	3 (1.6)
Hypochondroplasia	2 (1.2)	2 (1.2)	0
SHOX deficiency disorder	2 (1.2)	1 (0.6)	1 (0.6)
Chronic pediatric diseases	14 (7.8)	5 (2.8)	9 (5)
Celiac disease	6 (3.4)	1 (0.6)	5 (2.8)
Malnutrition and other chronic diseases (asthma, anemia, renal tubular acidosis, hypophosphatemic rickets, Duchenne, krabbe)	8 (4.4)	4 (2.2)	4 (2.2)
Psychosocial deprivation	2 (1.2)	1 (0.6)	1 (0.6)
Total	179 (100)	99 (55)	80 (45)

FSS: familial short stature, CDGP: constitutional delay of growth and puberty, IUGR: intrauterine growth retardation, T1D: type 1 diabetes mellitus.

Table 2
Characteristics of children with growth hormone deficiency.

	Total	Boys	Girls
Number (%)	77 (100)	51 (66.2)	26 (33.7)
Mean age at diagnosis (years \pm SD) [range]	8.2 \pm 4.38 [1.5–17.5]	8.52 \pm 4.55 [1.5–17.5]	7.62 \pm 3.98 [1.5–16]
Height at SDS onset [range]	-2.72 \pm 0.96 [-5; 0]	-2.86 \pm 0.91 [-5;-0.75]	-2.4 \pm 0.99 [-4; 0]
Height in SDS groups, n(%)			
\leq -4SDS	13 (16.9)	10 (13)	3 (3.9)
]-4;-2 [39 (50.7)	28 (36.4)	11 (14.3)
\geq -2 SDS	25 (32.5)	13 (16.9)	12 (15.6)
Target height SDS, n(%)			
<-2SDS	11 (14.3)	8 (10.4)	3 (3.9)
\geq -2SDS	66 (85.7)	43 (55.8)	23 (29.9)
Bone Age (years \pm SD)	5.92 \pm 3.68	6.18 \pm 4.03	5.37 \pm 2.86
Bone age-CA(years \pm SD) [range]	-2 \pm 1.4 [-6; 0]	-2.12 \pm 1.37 [-4.9; 0]	-1.7 \pm 1.52 [-6; 0]

SDS: Standard deviations, CA:chronological age.

celiac disease was the main chronic disease (n = 6, 3.4%).

Eighty patients in our study received GH treatment, which includes 51/77 patients with GHD, 23/43 children with IUGR, 7/8 girls with Turner syndrome, one child with Seckel syndrome, and one child with confirmed SHOX deficiency disorder. Thirty-three patients, that is, those with GHD (26/77), IUGR (6/43), and Turner syndrome (1/8) were lost to follow-up before the beginning of GH therapy because of bad socioeconomic conditions and difficulties to receive insurance coverage for their treatment.

4. Discussion

ST is one of the most common reasons for referral to pediatric endocrinology clinics [3]. Determining its profile in a country is thus important to consider. To the best of our knowledge, there are no previous Tunisian studies focusing on characteristics and etiologies of ST in children. Our cohort is also the largest one analyzed in Northern Africa.

In this study, it appears that the diagnosis of ST was overestimated in patients referred to our pediatric endocrinology clinic. Indeed, 45.5% of these children had normal height at first evaluation, and most of them (80.8%) were referred by general practitioners. This rate is greater than that in previous reports in Kuwait and Thailand, where, respectively, 20% and 10% of patients referred with ST had normal heights [7,12]. This high rate of false-positive diagnosis in our study would result from inaccurate height measurement or errors made when plotting growth parameters on growth curves or inaccurate analysis of growth chart.

These results are very important to note and highlight the need to teach our primary care physicians the right methods for measurement of growth parameters and analysis of growth chart. This may help to reduce the number of children inappropriately referred for assessment of ST and avoid unnecessary investigations, and possible psychosocial impact on them [13–15].

Interestingly, the percentage of patients with normal variants of growth in our study (5%) was much lower than that of patients with pathological ST (95%), and endocrine disorders were the predominant causes (47.5%). These findings differ largely from those reported in previous studies where normal variants of growth have been reported to be the most common etiologies of ST (40%–85%) [8,16–19], while endocrine disorders have been demonstrated to be a rarer cause (1.5–21%) [8,16–18]. This disparity between our results and others may be due to recruitment bias, as patients in our study were recruited in a pediatric endocrinology clinic, while those in other studies were population based. This hypothesis is very likely, as other studies conducted in endocrinology units have demonstrated results slightly similar to our study results, with predominant endocrine disorders ranging from 33.3% to 69%

[20–23].

GH deficiency was the most common cause of ST in our study and accounted for 43% of all etiologies and 90.6% of endocrine disorders. Similar findings were reported in Pakistan and Jordanian studies, where GHD was diagnosed in 69% and 69.1% of ST cases [20,24]. However, the percentage of GHD as a cause of ST in most of the previous studies was at least twice less important than that in our report, ranging from 2.4% to 23.4%. Most of these studies were conducted in specialized centers [5,6,25–29].

GHD was significantly more common in boys than in girls with a sex ratio of 1.96 (p = 0.02). This male predominance have been reported in previous Tunisian and Algerian studies [9,29,30] as well as in many other reports [25,26,31,32].

Moreover, children with GHD in our study were taller at the time of diagnosis (mean height SDS: -2.72 \pm 0.96) than other patients from Tunisia (mean height SDS: -2.98) [9] and Algeria (mean height SDS: -3.56) [29].

These differences may be due to an earlier age of referral in our study than that in the Tunisian study (mean age at diagnosis: 8.2 vs. 13.02 years [9]) and/or due to better monitoring of children's growth in our study than in the other Tunisian and Algerian studies, allowing for an earlier diagnosis [9,29].

The second endocrine cause of ST in our study was hypothyroidism, which was a rare cause accounting for only 4% of all etiologies. This proportion was lower than that in most of the previous reports, where hypothyroidism was found in 7.8%–17.2% of children with ST [6,21,22,25–28].

Regarding the nonendocrine causes of ST in our study, IUGR was by far the most common etiology (24%), which was greater than that in most of previous reports where IUGR accounted for less than 10% of causes of ST [5,7,8,12,20,26,28,30]. This result highlights the importance of a good evaluation of auxological parameters of all children at birth, which must be recorded in the Child Health Records Booklet.

On the other hand, genetic syndromes, mainly Turner syndrome, chronic pediatric diseases, skeletal dysplasia, and psychosocial deprivation were rarer causes of ST in our study, which was in agreement with some previous Iranian and Indian studies [23,25,27].

5. Conclusion

To summarize, we have demonstrated in this study that ST was largely overestimated (45.5%). Therefore, it is important to insist on adequate measurement and analysis of growth parameters since the birth to make an accurate diagnosis and avoid unnecessary investigations. GHD and IUGR were by far the most common causes of ST in our study. Celiac disease, although frequent in our country,

have not been found as a major cause of ST. However, given that this study was conducted at a sole pediatric department in pediatric endocrinology clinics, even though the major one, our findings may not reflect the true frequency of different etiologies in our population. Thus, further national multicenter studies are needed to establish the above-mentioned etiological profile of ST in Tunisia.

Conflicts of interest

All the authors report no conflicts of interest in this work.

Statement of human and animal rights

Our study has been reviewed by the hospital's ethics committee and has therefore been performed in accordance with the ethical standards laid down in an appropriate version of the 1964 Declaration of Helsinki.

Statement of informed consent

All the persons cited gave their consent before their inclusion in the study. Details that might disclose identity of the subjects under study have been omitted.

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Authors' contribution

All the authors listed met the 4 criteria defined by the ICJME and are thus designated as the authors of the manuscript.

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