The Etiological Spectrum of Short Stature among Children Attending Endocrine Clinic at Tertiary Care Hospital

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Abstract

Background: One of the most frequent reasons for referral to pediatric endocrinology units is short stature. Children's short height has a complicated etiology that includes genetics, race, gender, nutrition, and several endocrine hormones.

Objective: To determine the etiological spectrum of short stature among children presenting to endocrinology outpatient clinics in a tertiary care hospital.

Methods: This descriptive cross-sectional study was performed in the outpatient clinic of the Endocrinology Department at the National Institute of Child Health Hospital from September to December 2022. Short stature was defined as height for age <-2 standard deviations for the corresponding age and gender according to World Health Organization growth charts. 263 children were enrolled in the study. Detailed history and panel investigation for short stature were mediated for each child.

Results: A total of 263 patients were enrolled in the study having a median age of 8 (IQR=6-9) years and the majority were females (53.2%). The median SD of height and current weight was -3.48 (IQR= -4.3 - -2.83) and -2.8 (IQR= -3.59 - -2.17) respectively. The most frequently seen classification of short stature was the normal variant (68.1%) followed by endocrine disorders (19.8%), dysmorphic syndrome (9.9%), and chronic disease (2.3%). The most common cause of short stature was familial short stature (47.9%) followed by growth hormone deficiency (18.3%), constitutional short stature (9.1%), Turner syndrome (9.1%), both familial and constitutional SS (8%), idiopathic short stature (3%), celiac disease (2.3%), Cushing syndrome (n=2, 0.8%), panhypopituitarism (0.8%) and Seckel syndrome (0.8%).

Conclusion: This study analyzed that the majority of short stature are normal variants. However, findings of endocrine disorders, dysmorphic disorders, and chronic disease suggest timely screening and detection of short stature to avoid serious consequences of silent underlying diseases.

Keywords: *Short stature, pediatric endocrinology, growth hormone deficiency, Turner's syndrome, Cushing syndrome.*

INTRODUCTION

The complex biologic process of growth is influenced by various genetic, hormonal, dietary, and psychosocial factors working together. Short stature (SS) may be the result of any of these parameters being disturbed [1]. When a person has a small height, their height falls within the third percentile of the mean height for their age, sex, and demographics [2]. Biochemical, radiological, dietary, hormonal, and bone age assessments are all necessary for the diagnosis of SS. The main goals of treating ST are to tackle the underlying causes and the associated mental distress [3].

Pediatric patients should have their growth monitored, which is a well-accepted practice. Unnaturally slow or fast growth can be a sign of significant illnesses such as genetic disorders, chronic diseases, infectious diseases, abuse, or neglect. One of the most prevalent conditions for referral to pediatric endocrinology centers is SS, which affects 2-8% of various populations [4].

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Although not a disease in itself, short height is a symptom of several illnesses [5]. A normal variety of growth, such as familial SS and constitutional growth delay, is frequently linked to SS [6, 7]. Distinguishing these normal variants from a subset of atypical growth patterns brought on by pathogenic processes is a clinical difficulty [8].

According to studies, children with small statures have varied degrees of behavioral adaption disorder, stunted puberty, mental retardation, and psychological barrier in addition to height-related issues [9]. Parents could be worried and concerned. It is impossible to overstate the psychosocial strain on both parents and children [10].

Since factors such as race, lifestyle, diet, culture, and financial status have an impact on growth, it is believed that the causes of ST in children vary between industrialized and developing nations. Additionally, the type of the underlying disorder's nature and the likelihood of recovery. Determining the prevalence of various etiologies contributing to low stature in our population is therefore vital. Similar studies have, however, previously been carried out in Pakistan, but many of them suffer from the limitation of a small sample size, which is why we sought to carry out this study. The goal of this study

is to identify the range of etiologies contributing to low stature in children who visit outpatient clinics in a tertiary care facility.

MATERIAL AND METHODS

Between September to and December 2022, the National Institute of Child Health Hospital's Endocrinology Department conducted this descriptive cross-sectional study in its outpatient clinics. Before the study could begin, the ethical committee had to approve the study protocol. This study included patients with a confirmed diagnosis of SS between the ages of 6 and 17. Children with behavioral, neurological, or malnutrition issues were not allowed to participate. After receiving their parents' written consent, study participants were accepted into the study. To recruit study participants, a non-probability consecutive sampling technique was adopted.

Web-based calculator Using Open-Epi, the sample size was calculated using the following parameters; 55.9% major etiology frequency, 95% confidence interval, and 6% precision [11]. 263 was the estimated sample size. Short stature was defined as height for age < -2 standard deviation for the matching age and gender [2]. World Health Organization growth charts used weight for age and height for age. Patients with short stature who visited outpatient clinics had thorough medical testing to determine the cause of their short height.

The hallmarks of familial short stature (also referred to as genetic short stature) include bone age appropriate for chronologic age, normal growth velocity, and predicted adult height appropriate to the familial pattern (using the Bayley-Pinneau or Tanner-Goldstein-Whitehouse tables). By contrast, constitutional growth delay is characterized by delayed bone age, normal growth velocity, and predicted adult height appropriate to the familial pattern.

Laboratory studies used to assess the major causes of short stature in children include the following:

- Measurement of serum levels of insulin-like growth factor-I (IGF-I), formerly named somatomedin C, and IGF binding protein-3 (IGFBP-3)
- Karyotype by G-banding
- Measurement of serum levels of growth hormone (GH)
- Chromosomal study (karyotype)
- Bone age X-ray testing

Genetic syndromes, such as achondroplasia, CHARGE syndrome, Cornelia de Lange syndrome, 22q11.2 deletion syndrome, and Downs syndrome were ruled out. Celiac disease was diagnosed based on anti-tissue-transglutaminase antibodies (TTG IgA) > 10 U/mL. Cushing's syndrome is diagnosed by bilateral inferior petrosal sinus catheterization with a corticotrophin-releasing hormone (CRH) test. Panhypopituitarism was diagnosed as a deficiency of >3 anterior pituitary hormones. Seckel syndrome was considered

Table 1: Descriptive statistics for patients' features.

Variables	Frequency (%)
Age Groups	
1-5 years	43 (16.3)
6-10 years	185 (70.3)
11-14 years	35 (13.3)
Gender	
Male	123 (46.8)
Female	140 (53.2)
Gestational Age	
Full term	239 (90.9)
Preterm	24 (9.1)
SD of Height	
-2 to -3	87 (33.1)
<-3	176 (66.9)
SD of Weight	
>-2	65 (24.7)
-2 to -3	95 (36.1)
<-3	103 (39.2)

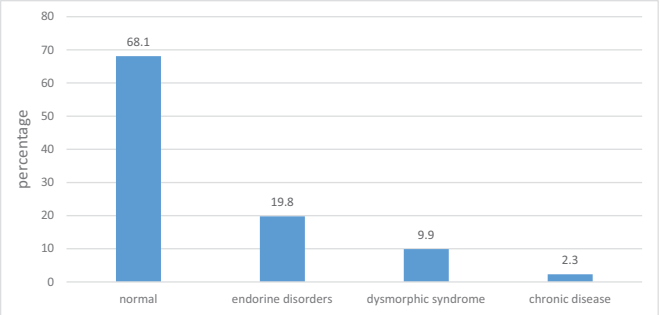

Fig. (1): Frequency of classification of short stature causes.

for postnatal dwarfism with severe microcephaly characterized by a "bird-like face", micrognathia, pointed nose, and receding forehead, associated with cognitive impairment.

The collected data was entered into SPSS version 21 for statistical analysis. Frequency and percentages were computed for categorical. Numerical variables were first assessed for normal distribution using the Shapiro-Wilk test. Chi-square test was applied to compare categorical variables among male and female gender. Non-normal numerical variables were compared using Mann Whitney U test. P-value less than or equal to 0.05 was considered as statistically significant.

RESULTS

A total of 263 patients were enrolled in the study having a median age of 8 (IQR=6-9) years. The age ranges from 1 to 14 years. All patients visited the clinic with complaints of improper growth and short height. Only 20% of cases were referrals from primary care clinics. Median birth weight and current weight were 2.2 (IQR=2.2-2.4) Kg and 18 (IQR=16-20) Kg respectively. The median SD of height and current weight was -3.48 (IQR= -4.3 - -2.83) and -2.8 (IQR= -3.59 - -2.17) respectively. Table **1** displays the features of the study participants.

Fig. (1) displays the classification of SS causes. Among all the causes, the most frequent cause was familial SS

Table 2: Comparison of age, height and weight, classification, and causes among males and females.

Variables	Male n(%)	Female n(%)	p-value
Age in years#	8 (6-9)	8 (6-10)	0.089
Height in SD#	-3.3 (-4.2 - -2.8)	-3.6 (-4.3 - -2.9)	0.082
Weight in SD#	-3.5 (-2.3 - -2.1)	-2.8 (-3.7 - -2.1)	0.702
Classification of causes			
Normal variant	93(75.6)	86 (61.4)	ǂ*0.041
Endocrine disorders	17(13.8)	35 (25)	
Dysmorphic syndrome	12(9.8)	14 (10)	
Chronic disease	1(0.8)	5 (3.6)	
Causes			
Familial short stature	72(58.5)	54 (38.6)	*0.001
Constitutional short stature	9(7.3)	15 (10.7)	0.340
Both familial and constitutional	10(8.1)	11 (7.9)	0.935
Growth hormone deficiency	15(12.2)	33 (23.6)	*0.017
Idiopathic short stature	2(1.6)	6 (4.3)	ǂ0.290
Turner Syndrome	0(0)	24 (100)	0.739
Celiac disease	1(0.8)	5 (3.6)	ǂ0.219
Cushing Syndrome	1(0.8)	1 (0.7)	ǂ1.000
Panhypopituitarism	1(0.8)	1 (0.7)	ǂ1.000
Seckel syndrome	0(0)	2 (1.4)	ǂ05.00

#Non-normal numerical variables are presented as median with inter-quartile range, ǂFisher-exact test was reported, *Significant at p<0.05

(n=126, 47.9%) followed by growth hormone deficiency (n=48, 18.3%), constitutional SS (n=24, 9.1%), Turner syndrome (n=24, 9.1%), both familial and constitutional SS (n=21, 8%), idiopathic (unidentified) SS (n=8, 3%), celiac disease (n=6, 2.3%), Cushing syndrome (n=2, 0.8%), panhypopituitarism (n=2, 0.8%) and Seckel syndrome (n=2, 0.8%).

Table **2** shows the comparison of patients' features and SS classification of causes among male and female patients. The frequency of the normal variant was significantly higher among males than females. Females had a significantly higher frequency of endocrine disorders. Familial SS was higher among males than females. The majority of females had SS due to growth hormone deficiency than males.

DISCUSSION

With socioeconomic advancement, the issue of children's growth has recently attracted more and more attention. To improve the result, it is crucial to comprehend the factors that affect growth and take preventive action. The social stigma, several treatable diseases, and ST that can cause psychological stress may all be seen as the tip of the iceberg. Therefore, early detection of short height is crucial because short height treatment is only successful before epiphyseal fusion.

This study found that the median age of patients visiting for short height evaluation was 8 years and the most frequent age group was 6-10 years. Another similar study from Syria also reports mean age of 8.8 ± 2.7 years with the most frequent age group of 6-8 years [12]. Essaddam *et al.* reported mean age of 8.2 ± 4.38 at the time of diagnosis [13]. A mean age of 9±4.18 years was reported in a similar study [14]. The frequent presentations in the age group of 6-10 years make sense as in younger ages, particularly in 1-4 years it is difficult for parents to identify the issue of small stature when children's height are already short. Growing older from 6 to 10 years does not cause an increase in their height brings the attention of parents and then they seek healthcare practitioners' opinions to rule out medical reasons.

ST can be a variation of healthy growth or the result of a sickness. Some growth issues are hereditary, while others may be brought on by hormone imbalances or inadequate nutrient intake. Causes for growth problems usually fall into the following categories; genetical, endocrinological, non-pathological, and chronic diseases. In our study, some of the patients were referred by primary care physicians to rule out the endocrinological cause of ST. Interestingly, none of the patients was misdiagnosed by a primary care physician for having ST. In contrast to our findings, studies conducted outside Pakistan reported a false positive rate of ST among primary care physicians [6, 13, 15].

Even though this study was conducted in an endocrinology outpatient clinic, the most frequent type of ST was a normal variant rather than an endocrinological cause. This finding is consistent with another study from Bangladesh which was also conducted in an endocrinology clinic and reported normal variant growth as the most frequent etiology among all types of ST [16]. Another similar study from Egypt also demonstrated that the normal variant was the most frequent etiology (61.6%) [5]. In contrast to our findings, endocrine disorders (57.5%) were the most frequent etiology, reported in a Tunisian study [13]. This study was conducted in a pediatric endocrinology unit and the majority of the patients were referred to this clinic for evaluating the endocrinological cause of SS which may elevated the count of endocrine disorders in this study. However, our study was also conducted in the pediatric endocrinology unit but endocrine disorders were not the most dominant cause as the majority of patients visiting endocrine disorders for primary consultations and a small proportion of patients were referred from primary care clinics. Uncommon etiological classification in our study was dysmorphic syndrome and chronic disease which is in agreement with other similar existing literature [5, 13, 16].

Overall the frequent cause in this study was familial SS. In familial SS, the height of children is consistent with parental height in the absence of nutritional, hormonal, acquired, genetic, and iatrogenic causes. This finding is in agreement with many other previous studies [5, 12, 16]. Among normal growth variants, the second topmost cause was constitutional growth delay. CGD is distinguished by normal growth rates, delayed

bone age, and expected adult height consistent with the familial pattern. Most CGD patients have a first- or second-degree relative who also has late puberty and CGD [17]. Some of the patients in our study had a coexistence of CGD with FSS. The existing literature consistently reports the coexistence of CGD with FSS in small proportions [5, 13, 14].

The second most cause irrespective of etiological classification and the top cause according to etiological classification of endocrine disorders in this study was growth hormone deficiency. Jasim *et al.* [14] also reported GHD as the second most cause in their study (7.4%). Karim *et al.* [16] detected GHD among 8% which was the third most common cause in his study. In contrast to our findings, a higher proportion of GHD deficiency was reported in the Tunisian study [13]. The most likely reason for the higher GHD rate in this study was conducted in the pediatric endocrinology unit and the majority of patients were referred to this clinic by primary care physicians to rule out endocrine disorders. Panhypopituitarism was an uncommon cause of SS in our study which is consistently reported as a rare etiological factor in SS patients [5, 13, 16].

ST is one of the major components of many dysmorphic syndromes [18, 19]. In this study, we found that few patients had dysmorphic disorders including Tuner's syndrome and Seckel syndrome. The existence of dysmorphic disorders is also reported in a few patients of SS in previously existing studies [5, 12, 13].

According to the nature and progression of the illness, chronic disease adversely impacts growth, and the resulting impairment in height may be temporary or permanent [20]. In this study, we found that a smaller proportion had celiac disease which is a line finding with similar studies [5, 13].

The present study documents a single-center experience with limited sample size. For validation of the findings of the current study, we recommend conducting a larger multi-center study.

CONCLUSION

This study analyzed that the majority of short stature are normal variants. However, findings of endocrine disorders, dysmorphic disorders, and chronic disease suggest timely screening and detection of short stature to avoid serious consequences of silent underlying diseases.

ETHICAL APPROVAL

This study was first approved by the Hospital Ethics Committee National Institute of Child Health (NICH), Karachi, Pakistan (IERB-24/2022) before its commencement. All procedures performed in studies involving human participants were following the ethical standards of the institutional and/ or national research committee and with the Helsinki Declaration.

CONSENT FOR PUBLICATION

Written informed consent was taken from all the parents of all patients.

AVAILABILITY OF DATA

The data will be available from the corresponding author upon a reasonable request.

FUNDING

Declare none.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Declared none.

AUTHORS' CONTRIBUTION

HUI conceptualized the study. MI designed the study. KS and ZS were involved in data collection. HUI and ZS performed data analysis. HUI and KS prepared initial draft of the manuscript. MI critically revised and reviewed the initial draft. All authors read and approved the manuscript.

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