Etiological Profile of Short Stature in Children and Adolescents

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Abstract

Context: The delayed growth of a child is a major cause of concern for the parents. There is a multitude of etiological factors which must be considered in relation to this common aspect of healthcare. **Aim:** The study was done to evaluate the etiological profile of short stature in children and adolescents. **Settings and Design:** The cross-sectional study was conducted for 12 months including 111 cases of short stature (out of the 1,058 cases screened), at the endocrinology outpatient department (OPD) of a tertiary care institute in Haryana. **Subjects and Methods:** As per the inclusion criteria, cases with age <18 years were enrolled. The examination and anthropometric measurements were performed in the presence of parents/guardians. **Results**: Out of the 1,058 cases screened; 111 cases of short stature were recruited as per the inclusion and exclusion criteria. The prevalence was about 10.49% of the total population. The mean age of the sample was 12.34 ± 3.19 years. The endocrine causes were the most common followed by normal variants of growth and delay, chronic systemic illness, and nutritional and skeletal causes. Among the endocrine causes, hypothyroidism was the most common followed by growth hormone deficiency and type 1 diabetes mellitus (T1DM). **Conclusions**: The mean chronological age of 12.34 ± 3.19 years suggests the delayed detection of short stature in the population. This highlights the importance of educating parents so that timely therapeutic intervention can be done to achieve the potential height.

Keywords: Constitutional delay of growth and puberty, familial short stature, growth hormone deficiency, idiopathic short stature

INTRODUCTION

Short stature is defined as a height of less than the 3rd percentile or 2 or more standard deviations (SDs) below the mean height for age and gender.[1] There is a multitude of etiological factors which must be considered in relation to this common aspect of healthcare. The causes are broadly classified into normal variants and pathological causes. The normal variants including familial short stature and constitutional growth delay (CGD) are the commonest. The pathological causes include endocrine diseases, chronic diseases, metabolic diseases, and clinically defined syndromes.[2,3]

Therefore, the present study was planned considering its impact on the healthcare of children and adolescents.

SUBJECTS AND METHODS

The present cross-sectional study was done at the endocrinology outpatient department (OPD) of a tertiary care institute to evaluate the etiological profile of short stature in children and adolescents in Haryana. The study was conducted for 12 months after approval from the institutional ethics committee. As per the inclusion criteria, cases of either gender with age less than 18 years and a height less than the 3rd percentile for age and gender or growth velocity less than the 25th percentile were enrolled. The written informed consent was obtained from the parents/guardians before the inclusion of the cases into the study. The cases with contractures and deformities, fused epiphysis on hand X-ray, and cases under treatment from the outside hospital were excluded from the study. A total of 1,058 cases of short stature were screened, and 111 cases were recruited for the study based on the inclusion and exclusion criteria.

The examination and all anthropometric measurements were performed in the presence of the parents/guardians after informed consent. The height (H) was measured in centimeters

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using a stadiometer and recorded on the the Indian Academy of Pediatrics-World Health Organization (IAP-WHO) growth chart. The body weight (W) was measured in kilograms with the help of an electronic balance. The body mass index (BMI) was calculated by dividing the weight (kilograms) by the square of the height (meters). The lower segment was measured by a vertical ruler as the distance from the top of the symphysis pubis to the floor. The upper segment was derived by subtracting the lower segment from the total height, and the ratio of the upper and lower segment was calculated.

The mid-parental height (MPH)/target height (TH) was calculated using the following formula:
- MPH for boys = (mother's height + father's height)/2 + 6.5 cm ± 8 cm
- MPH for girls = (mother's height + father's height)/2 – 6.5 cm ± 8 cm

The detailed history, family history of short stature, and parental age at puberty were enquired from each case. The general physical examination and routine investigations were done in all the cases. The X-ray of the non-dominant (left) hand with the wrist joint was done for determining the bone age using Greulich and Pyle's atlas of skeletal development.[4] The height age was determined as the age which corresponded to the height in centimeters along the 50th percentile curve on the growth chart. The sexual maturity rating and stages of puberty were recorded based on Marshall and Tanner's staging.[5,6]

The serum follicle-stimulating hormone test (measured by chemiluminescence immunoassay, Immulite-1000, Siemens) was done in all the females presenting with short stature. The thyroid function tests were done to detect hypothyroidism. The serum thyroid-stimulating hormone (TSH) was measured by immuno-radiometric assay (IRMA, Immunotech, Beckman Coulter). The serum T3 (triiodothyronine) and T4 (tetraiodothyronine) were measured by radio-immunoassay (RIA, Immunotech, Beckman Coulter). The growth hormone deficiency (GHD) was diagnosed if the peak serum growth hormone levels were <10 ng/L after growth hormone stimulation (estimated by chemiluminescence immunoassay, Immulite-1000, Siemens) and low-serum insulin-like growth factor-1[7] (measured by chemiluminescence immunoassay, Immulite-1000, Siemens). The growth hormone stimulation was done by tablet clonidine (0.15 mg/m^2). The diagnosis and assessment of the severity of anemia were done based on the cut-off defined by the WHO).[8] Severe anemia was defined as a hemoglobin level of less than 7 g/dL in children under 5 years of age, and less than 8 g/dL for children over 5 years of age.[8]

The familial short stature (FSS) was diagnosed if a child was short in comparison to the reference population but remained within the range of the TH with no bone age delay and normal growth velocity.[9] The constitutional delay of growth and puberty (CDGP) was detected by the presence of short stature, bone age delay (≥2 years), delayed puberty (onset at ≥13 years in girls and ≥14 years in boys) with normal growth velocity, and

family history of delayed puberty.[9] Whereas, the idiopathic short stature (ISS) was detected by the presence of a subnormal growth rate, delayed bone age without any apparent medical cause for growth failure, and normal growth hormone response to provocative testing.[10]

The data analysis was done using a statistical package for social sciences (SPSS) version 21.0. The normality of the data was tested by the Kolmogorov–Smirnov test. If the normality was rejected; then a nonparametric test was used. The quantitative variables were compared using the independent t-test/Mann–Whitney test (when the data sets were not distributed normally) between the two groups. The qualitative variables were correlated using the Chi-square test/Fisher's exact test. A *P* value of <0.05 was considered statistically significant.

Results

In the present cross-sectional study, out of a total of 1,058 cases screened; 111 cases were diagnosed as having short stature. The recorded height and weight of the study subjects were plotted on the growth charts. The calculated prevalence of short stature was about 10.49% of the total population.

The males 50.45% (56 cases) with mean age 13.3 ± 3.03 years were found to be affected slightly more than the females 49.55% (55 cases) with mean age 11.36 ± 3.08 years. A significant difference was seen in the age distribution between the males and females (*P* 0.016). The majority of the females were in the age group less than 12 years; whereas the majority of males were more than 12 years. The observed mean (SD) of the chronological age (CA) of the sample was 12.34 ± 3.19 years. The mean (SD) values of height (H), weight (W), height age (HA), and bone age (BA) of the study subjects are listed in Table 1.

Among the 111 subjects diagnosed as having short stature, the endocrine causes were found in 42.34% of the cases. Among the endocrine causes, the most commonly observed etiology was hypothyroidism accounting for 30.63% of the cases [Table 2]; where the females (38.18% cases) were found to be affected more than the males (23.21% cases) with no significant difference (*P* 0.053). The ISS, i.e., where no pathology was found (including familial and constitutional delay) was found to be present in 43 cases (38.74%); among them, FSS was seen in 35 cases (31.53%) while CDGP was found in 8 cases (7.21%). The GHD was found in 8.11% cases (12.50% males and 3.64% females with a non-significant difference; *P* 0.085). Type 1 diabetes mellitus (T1DM) was found to be present in 7.21% of the cases (12.73% females and 1.79% males with a significant difference; *P* 0.02).

Chronic systemic illness (CSI) as the cause of short stature was found among 38 cases (34.23%). In this group, a majority of the cases were related to celiac disease (29 cases; 26.13%). The hemoglobinopathies (thalassemia major) were seen in 6.31% of the cases followed by bronchial asthma in 2.70% of the cases and congenital heart disease (CHD) in 1.80% of the

Table 1: Auxological parameters of study subjects (sample size=111)

Parameter	Mean (SD)*	Median (IQR)†	Min-Max
Chronological age	12.34±3.19	12.83 (10-15)	3.83-17.5
Height	127.25±14.53	130 (115-138.750)	85.7-153.5
Weight	28.75±7.98	28 (22.250-35)	10-53
BMI‡	17.37±2.18	17.1 (16-18.550)	13.3-25.2
BW§	2.31±0.33	2.4 (2-2.500)	1.5-3
Height age	8.09±2.45	8.42 (6-10.125)	2.17-13.42
Bone age	9.98±3.14	10 (8-12.375)	2-16
Mid-parental height	147.77±5.96	149 (142-151.750)	134.6-159.5

*SD: standard deviation; †IQR: inter-quartile range; ‡BMI: body mass index; §BW: birth weight

Table 2: Frequency distribution of different etiology of short stature

Category	Frequency	Percentage
Idiopathic short stature	43	38.74%
Familial short stature	35	31.53%
CDGP*	8	7.21%
Chronic systemic illness	38	34.23%
CHD†	2	1.80%
Bronchial asthma	3	2.70%
Celiac disease	29	26.13%
Thalassemia major	7	6.31%
Chronic renal failure	1	0.90%
Nutritional cause	7	6.31%
Malnutrition	2	1.80%
Severe anemia	2	1.80%
Rickets	3	2.70%
Endocrine causes	47	42.34%
Hypothyroidism	34	30.63%
GHD‡	9	8.11%
TIDM§	8	7.21%
Skeletal	1	0.90%
Achondroplasia	1	0.90%

*CDGP: constitutional delay of growth and puberty; †CHD: congenital heart disease; ‡GHD: Growth hormone deficiency; §TIDM: Type 1 diabetes mellitus

cases in decreasing order of frequency. The next important cause of short stature was nutritional disorders (6.31% cases); among them, rickets was found in 2.70% of the cases followed by severe anemia and malnutrition in two cases each (1.80%). The skeletal causes were present in 0.90% of the cases as achondroplasia [Table 2].

Among the 111 subjects diagnosed as short stature, 95.50% (106 cases) were having proportionate short stature; while only about 4.50% (5 cases) were having disproportionate short stature. Among the cases of short stature with hypothyroidism (30.63%), an equal ratio of the upper and lower body segments was observed in 9.80% of the cases while 76.19% of the cases were having a ratio >1 and 33.33% of the cases had a ratio <1 with a significant difference in observations (*P* 0.0001). Among the cases of short stature

with GHD (8.11%), an equal ratio of the upper and lower body segments was observed in 1.96% of the cases while 20.51% of the cases were having a ratio <1 with a significant difference in observations (*P* 0.002).

Among 26.13% of the subjects with short stature in whom celiac disease (CD) was found; 26.47% of the cases were associated with hypothyroidism while no association was observed between the two in 25.97% of the cases; with no significant difference seen in the observations (*P* 0.956).

Among 7.21% of the subjects with short stature in whom T1DM was found, 8.82% of the cases were associated with hypothyroidism. Among 26.13% (29 cases) of the subjects with short stature in whom CD was found, 87.50% cases were associated with T1DM while no association was observed between the two in 21.36% of the cases, with a significant difference in the observations present (*P* 0.0003).

DISCUSSION

The delayed growth of the child is a major cause of concern for the parents. The short stature, itself, is a manifestation of many underlying diseases. A delay in the diagnosis and initiation of treatment for these underlying disorders may result in the failure to achieve the genetic potential in height. Therefore, early diagnosis and intervention carry important significance to address the problem of short stature.

The available studies reflect a different prevalence of short stature based on geographical, environmental, and socioeconomic factors. In the present study, the calculated prevalence of short stature was about 10.49% of the total population. The endocrine causes were the most common cause of short stature, of them, hypothyroidism was the most common followed by GHD and T1DM. The extent of the short stature as reflected in this study (a prevalence of 10.49%) was higher than reported by Colaco[11] (prevalence of 5.6% in 2,500 children admitted in hospitals and 10% in children attending outpatient services). However, Garg[12] (out of a total of 625 children screened with age 3–15 years attending OPD of a community-level hospital; 86 cases were identified as having short stature) had reported 13.8% prevalence of short stature, higher than that of our study (out of a total of 1,058 cases screened, 111 cases were diagnosed as having short stature with a prevalence of 10.49%).

The assessment of short stature before the epiphyseal fusion is a prerequisite for timely medical management. Unlike the previous Indian studies, the maximum number of short children presented in the 9–15 years age group (64.56%). This reflects the lack of awareness regarding the problem of short stature among the general population. Bhadada,[13,14] *et al.* reported normal variants as the predominant cause of short stature. Also, they observed pituitary disorders in 19.2%, CD in 13.7%, and hypothyroidism among 13.7% of the cases of short stature in 2005–2007,[13] compared to their findings of hypothyroidism in 18.4%, pituitary

disorders in 15.21%, and nutritional disorders in 17.4% of the cases of short stature in 1995–1996.[14] The prevalence of hypothyroidism (30.63%) in our study was higher than that reported by Bhadada *et al*[14]. (18.4%). This variation in the etiological profile could be due to a difference in the study population, geographical and social factors, and healthcare facilities. Bhadada *et al.* showed normal variants of growth and delay as the most common cause followed by endocrine causes; while endocrine causes were most common in our study followed by normal variants. The etiological profile of the two studies could not be compared because of the different sample sizes. Both studies were done in different populations and at different intervals.

Zargar,[15] *et al.*, from the department of endocrinology, Sher-I-Kashmir Institute of Medical Sciences, determined the causes of short stature in a retrospective study including 193 subjects. The GHD was the commonest identifiable cause of short stature accounting for 22.8% of the cases; in contrast to our study where hypothyroidism was the most common cause of short stature found in 34 cases (30.63%) while GHD was seen only in 9 cases (8.11%).

Thirty-six subjects (18.7%) had a normal variant short stature, while in our study, the normal variant as a cause of short stature was seen in 43 cases (38.74%). Al-Jurayyan,[16] *et al.*, 2012, reported a retrospective study of short stature cases referred to the pediatric endocrine clinic. Their study reported short stature as a common referral problem, with FSS being the commonest and seen in 57 (51.8%) patients while in the other 53 (48.2%) patients, variable endocrine and nutritional causes were noted. In our study, the endocrine causes were the commonest (42.34%), followed by normal variant short stature (38.74%).

Lashari[17] *et al.*, 2014, in a descriptive cross-sectional study conducted from January 2007 to July 2007, found CGD and FSS as the most common causes of short stature, accounting for 55% of all the short stature cases. They concluded that the most common etiological factors in the order of frequency were normal variants of growth (CGD, FSS), CSI, hypothyroidism, GHD, and CD. In our study, the most common etiological factors in the decreasing order of frequency were endocrine causes, normal variants of growth (CGD, FSS), CSI, and nutritional causes followed by skeletal causes.

Ullah[9] *et al.*, 2016, in a descriptive cross-sectional study described GHD, CDGP, FSS, and hypothyroidism as the most common causes of short stature in the decreasing order of frequency; while in our study, the maximum cases were related to normal variant short stature followed by hypothyroidism and GHD. The normal variant short stature was comparable in both the studies. A slight male preponderance was observed in both the studies. Hussein[18] *et al.*, 2017, in their descriptive observational study from May 2012 to December 2015 determined the frequency of etiological factors causing short stature. In our study, the cases of CD were higher while that of GHD were lower than

Hussein's study. They recommended that growth hormone treatment in children, however, should be promptly initiated with specific clinical indications.

The small sample size was the major limitation of this study. As the study was done at a tertiary care institute, the selected sample is not a true representation of the general population. This highlights the need for a large-scale population-based study for better representation of the problem of short stature in a defined geographical area.

The study results suggest that the frequency of endocrine causes is higher in the endocrine referral center. The mean CA of the study sample of 12.34 ± 3.19 years suggests delayed recognition of the problem in the population. This highlights the need and importance of educating parents along with the serial screening of height and weight to identify a significant growth delay in short children at an earlier age, so that timely therapeutic intervention can be done to achieve the potential height. The growth charts serve as an inexpensive tool for monitoring growth in children and promptly identify significant delays in growth. The study findings can frame our mindset to remain vigilant about the problem for detection at its earliest stage to achieve maximum benefit from the available treatment.

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Conflicts of interest
There are no conflicts of interest.

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