ORIGINAL ARTICLE

Etiology of Short Stature in Children

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ABSTRACT

Objective: To determine the causes of short stature in children with special emphasis on growth hormone deficiency.

Study Design: Case series.

Place and Duration of Study: Department of Paediatrics, Military Hospital, Rawalpindi and Combined Military Hospital, Multan from September 2004 to January 2007.

Methodology: Two hundred and fourteen children (140 boys and 74 girls), ranging from 02 to 15 years presenting with short stature were studied. Height and weight were plotted on appropriate growth charts and centiles determined. Relevant hematological and biochemical investigations including thyroid profile were done. Bone age was determined in all cases. Growth hormone axis was investigated after excluding other causes. Karyotyping was done in selected cases. Data was analyzed by SPSS 10.0 by descriptive statistics. Mean values were compared using t-test.

Results: In this study, the five most common etiological factors in order of frequency were Constitutional Growth Delay (CGD), Familial Short Stature (FSS), malnutrition, coeliac disease and Growth Hormone Deficiency (GHD). In 37.4% of patients, the study revealed normal variants of growth – CGD, FSS or combination of both, 46.7% cases had non-endocrinological and 15.9% had endocrinological etiology. CGD (22.1%) in males and FSS (27%) in females were the most common etiology. GHD was found in 6.1% children and it comprised 38.2% of all endocrinological causes. Children with height falling below 0.4th centile were more likely to have a pathological short stature (79.2%) compared to 39.3% whose height was below 3rd centile but above 0.4th centile (p<0.05).

Conclusion: CGD and FSS are most common causes of short stature in boys and girls respectively, whereas, GHD is a relatively uncommon etiology.

Key words: Constitutional growth delay.   Familial short stature.   Growth hormone deficiency.   Short stature.

INTRODUCTION

Short stature is a common problem in children globally, especially in developing countries.[1] When compared with well-nourished and genetically relevant population, short stature is defined as height or length below 3rd per centile for that age and gender.[2] Statistically, this refers to children who are shorter than 97% of their age and gender matched peers. Causes of short stature are diverse but fortunately the most common causes, beyond the first two years of life are Familial Short Stature (FSS) and Constitutional Growth Delay (CGD).[1,3,4] These are variants of normal growth and need no medical treatment, however, emotional stress associated with it should be alleviated.[5]

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Almost any chronic disease can cause short stature such as renal disease, malignancy, pulmonary disease, Cystic Fibrosis (CF), cardiac disease etc.[3,6] Coeliac disease is a prime example of a remediable cause of short stature, especially in younger children.[7] Nutritional deprivation and therapies like glucocorticoids, chemotherapeutic drugs, radiotherapy can result in short stature.[8] Common endocrinological causes of short stature include hypothyroidism, hypopituitarism (isolated GHD or multiple anterior pituitary hormone deficiencies), hypercortisolism and classical Laron syndrome.[3,6,9,10] All these are characterized by being overweight-for-height. Short stature may also be seen with severe Intrauterine Growth Retardation (IUGR) or children born Small for Gestational Age (SGA) and in large number of dysmorphic syndromes.[1,2,11] Idiopathic Short Stature (ISS) is considered when no causative disorder can be identified.[12]

In contrast to developed countries, data addressing the frequencies of different causes of short stature in Pakistan is not generous, though there have been a few studies focusing on the individual diseases. In comparison to western world, a wide range of factors like genetic and environmental factors, nutritional deficiencies and exposure to infectious diseases may be responsible for underlying etiology of short stature in our

country. The aim of this study was to find out etiological profile of short stature in children presenting in tertiary care military hospitals.

METHODOLOGY

This observational study was carried out over a period of 29 months from September 2004 to January 2007 at Paediatric Departments of two tertiary care hospitals - Military Hospital, Rawalpindi and Combined Military Hospital Multan, Pakistan. Children residing in Pakistan with short stature were enrolled. Inclusion criteria were age below 18 years, height more than 2 SD below the mean (< 3rd percentile), low growth velocity (< 4 cm/yr) or small for midparental height and adequate follow-up (at least for 6 months). Exclusion criteria were diagnosed cases of thalassemia major or other chronic diseases, as well as patients or their parents not willing to be included in the study.

Thorough history and physical examination were recorded on a predesigned proforma. Standing height without head or foot gear (measured with a stadiometer), upper to lower segment ratio, weight and head circumference were measured. For height measurement, head was positioned in Frankfurt plane, the head projection was placed at the crown of the head and the measurement was recorded to the nearest 0.1cm.[13] All efforts were made to record heights on subsequent visits on the same apparatus. Growth parameters were first plotted on 2000 CDC growth charts (developed by the American National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion)[14] and all those children with height below 3rd centile were included in the study after satisfying inclusion criteria. Furthermore, Nine Centile United Kingdom Charts were used to determine if the child height was below 0.4th centile which were introduced by Child Growth Foundation in 1994 with lowest centile being 0.4th centile.[15]

Nutritional assessment was done by using Waterlow method, weight for height, triceps skin fold and mid arm circumference. Stages of puberty were determined according to the classification of Marshall and Tanner. Detailed birth and family history was recorded including birth length and weight, parental heights, and the age of puberty for each parent. Mid parental height was calculated to identify the genetic growth potential. Relevant investigations were requested in the light of available information collected from history and clinical examination. Screening investigations included complete blood count, ESR, renal and thyroid function tests, glucose, calcium, phosphate, alkaline phosphatase, alanine aminotransferase and urinalysis. Bone age was determined in all cases by radiological assessment of the epiphyseal maturation or shapes of bones of the left hand/wrist or elbow in older children, comparing with Greulich Pyle charts.[16]

In every case, at least 6 months of growth monitoring was done. Frequencies of various causes were analyzed in general and in two age groups (under or above 05 years of age). Diagnosis of growth deviation in children was grouped as normal variants of growth and pathologic short stature including non-endocrine and endocrine disorders. Normal variants of growth included CGD (i.e. proportionate short stature, normal growth velocity and delayed bone age, bone age consistent with height age often with a family history of delayed pubertal development, or late adolescent growth spurt) and FSS (i.e. proportionate short stature with a normal growth velocity, normal bone age, and short mid-parental height).[17]

Non-endocrine systemic disorders were diagnosed by history, examination and appropriately selected laboratory tests. Cases of malnutrition were diagnosed after thorough inquiry regarding feeding, appropriate measurements and detailed workup for malabsorptive conditions. Regarding coeliac disease, when initial workup was unremarkable, additional investigation was performed by measuring the concentrations of serum IgA antigliadin, antireticulin and anti-endomysial antibodies. Children with positive serology, strong clinical suspicion or having IgA deficiency were subjected to diagnostic histopathologic examination of small gut biopsy. For the diagnosis of coeliac disease, the revised criteria by European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGAN) were followed.[18] Blood and urinary pH was determined in cases with suspected Renal Tubular Acidosis (RTA) and metabolic disorders. Hypothyroidism was diagnosed after determining serum T4, TSH levels and thyroid scans.

Enrolled children were monitored for about 06-12 months before going for Growth Hormone (GH) testing. GHD was confirmed if the peak GH concentration failed to reach 10 ug/L with two back to back provocative tests (L. dopa, exercise, clonidine or insulin).[19] Children born SGA and failing to achieve catch-up growth were investigated and subsequently growth velocity was monitored to rule out other causes. Idiopathic short stature was considered in children with short stature, low growth velocity, without any apparent medical cause and normal growth hormone response to provocative testing.[26] Karyotyping was carried out in those female subjects where the etiology was in doubt, to rule out Turner's syndrome.

Data was entered in SPSS version 10.0 and descriptive statistics were used to calculate frequencies of various causes of short stature according to etiological groups in two age groups. Variables were compared by using Chi-square and student's t-test. The value of $p < 0.05$ was considered to be statistically significant.

RESULTS

A total of 214 cases [140 males (65.4%), 74 females (34.6%)] were identified as having short stature, with mean chronological age of 6.1 $\pm$ 3.1 years, mean bone age of 5.0 $\pm$ 2.8 years, mean height of age 4.3 $\pm$ 2.6 years and mean growth velocity of 4.9 $\pm$ 3.5 cm/years. Among the study population, mean height was 99.6 centimeters ($\pm$15.4) and mean mid-parents height was 163.3 centimeters ($\pm$10.4). Male to female ratio was 1.9:1. All children fell below 3rd centile for their height on 2000 CDC growth charts, whereas, 125 patients (58.4%) had height below 0.4th centile on 1990 UK growth charts.

The frequencies of various causes of short stature in this study are shown in Table I. Three main etiological groups were identified. Non-endocrinological diseases as a group were the most common cause (46.7%) in comparison with normal variants of growth (37.4%) and endocrinological causes (15.9%). In males, 50% had non-endocrinological diseases, 33.6% were normal variants of growth while 16.4% had endocrinological diseases whereas, in females these values were 40.5%, 44.6% and 14.9% respectively. In this study, the five most common single etiological factors were CGD (17.3%), FSS (15%), malnutrition (9.8%), celiac disease (6.5%) and GHD (6.1%) as shown in Table I. In males,

Table I: Causes of short stature (n=214).

Etiology	Total n (%)	Male n (%)	Female n (%)
Normal variants of growth			
Constitutional growth delay (CGD)	37 (17.3%)	31 (14.5%)	6 (2.8%)
Familial short stature (FSS)	32 (15.0%)	12 (5.6%)	20 (9.3%)
FSS and CGD (co-existent)	11 (5.1%)	04 (1.9%)	07 (3.3%)
Endocrinological causes			
Growth hormone deficiency (GDH)	13 (6.1%)	08 (3.7%)	05 (2.3%)
Hypothyroidism	12 (5.6%)	09 (4.2%)	03 (1.4%)
Congenital adrenal hyperplasia (CAH)	03 (1.4%)	02 (0.9%)	01 (0.5%)
Laron syndrome	02 (0.9%)	02 (0.9%)	-
Diabetes mellitus	02 (0.9%)	01 (0.5%)	01 (0.5%)
Central diabetes insipidus	01 (0.5%)	-	01 (0.5%)
Non-Endocrinological causes			
Malnutrition	21 (9.8%)	14 (6.5%)	07 (3.3%)
Celiac disease	14 (6.5%)	10 (4.7%)	04 (1.9%)
Genetic syndromes	12 (5.6%)	08 (3.7%)	04 (1.9%)
Skeletal dysplasia and rickets	12 (5.6%)	08 (3.7%)	04 (1.9%)
IUGR/SGA	09 (4.2%)	07 (3.3%)	02 (0.9%)
Congenital heart disease (CHD)	08 (3.8%)	06 (2.8%)	02 (0.9%)
Storage disorders	04 (1.9%)	04 (1.9%)	-
Chronic anemia and malabsorption	04 (1.9%)	02 (0.9%)	02 (0.9%)
Renal tubular acidosis (RTA)	04 (1.9%)	03 (1.4%)	01 (0.5%)
Idiopathic short stature (ISS)	02 (0.9%)	02 (0.9%)	-
Psychosocial dwarfism	02 (0.9%)	-	02 (0.9%)
Chronic renal failure (CRF)	02 (0.9%)	01 (0.5%)	01 (0.5%)
Bronchial asthma	02 (0.9%)	01 (0.5%)	01 (0.5%)
Duchenne muscular dystrophy	02 (0.9%)	02 (0.9%)	-
Cerebral palsy	01 (0.5%)	01 (0.5%)	-
Cystic fibrosis (CF)	01 (0.5%)	01 (0.5%)	-
Bartter syndrome	01 (0.5%)	01 (0.5%)	-
Total	**214 (100%)**	**140 (65.4%)**	**74 (34.6%)**

CGD (22.1%) and in females FSS (27%) were the most common single etiological factor. A total of 11 cases (4 males and 7 females) had both FSS and CGD. Malnutrition and celiac disease were the leading non-endocrinological causes of short stature.

A total of 43.5% cases were below 05 years of age. Normal variants of growth were more common in children with age above 05 years; 60 out of 121 (49.6%), compared to 21 out of 93 (22.6%) children under 05 years of age (p<0.05). Non-endocrinological causes were more common in children with age under 05 years, 60 out of 93 (64.5%), in comparison to 40 out of 121 (33.1%) in children over 05 years of age (p<0.05). In cases with height falling below 3rd centile, 60.7% were variants of normal growth and only 4.5% were of endocrinological disturbance. The same values reduced to 20.8% and 24% respectively, in cases where height was falling below 0.4th centile. Among uncommon causes of short stature in this study were Turner syndrome (02), Down syndrome, Seckel syndrome (01), Hallermann Strieff syndrome (01), Russel Silver syndrome, Leri Weill dyschondrosteosis (02), Bartter syndrome, chronic renal failure, cystic fibrosis, poorly controlled asthma, insulin dependent diabetes mellitus, diabetes insipidus, glycogen storage disease type I, achondroplasia, metaphyseal dysplasia, mucopolysa-ccharidosis and Duchenne muscular dystrophy (02). Two males were finally labeled as idiopathic short stature, while two females had psychosocial dwarfism.

There were a total 13 (6.1%) cases of GHD in this study with male to female ratio 1.6:1, mean height was 104.4 $\pm$ 11.3 cms, mean age at the time of diagnosis was 7.8 $\pm$ 2.9 years, mean bone age was 4.5 $\pm$ 2.0 years and mean growth velocity was 2.9 $\pm$ 0.4 cm/year. All cases of GHD were diagnosed after suboptimal response to two consecutive GH stimulation tests. 84.6% of GHD cases had age more than 05 years and 92.3% were falling below 0.4th centile on nine percentile UK growth charts.[15]

DISCUSSION

Short stature has been studied extensively worldwide[17,20,21] but similar studies are quite few in Pakistan. As per definition of short stature, 3% of normal population falls in this category. Any child with an abnormally slow growth rate, height below 3rd percentile, or height considerably below the genetic potential deserves further evaluation. An assessment of growth requires reliable growth measurements with data plotted on suitable growth charts.[5]

Fortunately, majority of children with height falling below 3rd centile are part of normal population, with only a small number having endocrine abnormalities.[22,23] Shu *et al.* have documented in their studies that normal variants may comprise as much as 65% of the short

children.[22] In this study, the most common single etiology of short stature found was CGD, especially in boys. In contrast, FSS affected 27% of girls and only 8.6% boys. As a group, normal variants of growth (CGD and FSS) were responsible for 37.9% (17.3% CGD, 15% FSS and 5.1% having combination of both FSS and CGD) of short stature making it the leading cause of short stature in this study. This dominance of normal variants of growth is in accordance with other worldwide studies.[17,22,23] Thus, it is very important to remember that many cases of short stature in general population may be normal, as determined by meticulous measurements, and determination of bone age using standard charts and experts radiological opinion. Timely identification of such cases not only helps to avoid extensive and unnecessary investigations but also alleviates parental anxiety.

In this study, 46.7% of short stature children had non-endocrinological cause while endocrinological causes contributed only 15.9%. Out of those, 6.1% were previously unrecognized for GHD, almost same as reported by Bhadada *et al.* (7.4%) in Indian population and in Taiwan as 7.9%.[4,22] Some studies showed quite high frequency of GHD as in Iran it was reported 23.4% and 22.8% by Zargar *et al.*[3,17] Another study from Pakistan done at the Armed Forces Institute of Pathology, Rawalpindi (a referral center for endocrine studies), revealed frequency of GHD as 13.9% out of 273 children referred and tested for GHD.[24] It must be noted that these studies were conducted in the endocrine referral centers; therefore, the prevalence of endocrine disorders, especially GHD, is bound to be high in these studies. In fact, endocrinological contribution may be less than 4% in children with short stature. There is no worldwide consensus on the definition of GH deficiency but most paediatric endocrinologists use a cutoff serum GH concentration of 10 ug/L.[25] In this study, growth velocity was monitored in most cases, before going for GH testing and GHD was confirmed if the peak GH concentration was below 10 ug/L in two consecutive provocative tests.[19] In this study, GHD was more common in boys, which is in accordance to a study from Iran.[17] It may be due to more parental concern shown towards boys. Although the epidemiologic data indicates that all variants of normal growth are twice as common in boys as in girls. This gender difference may reflect greater concern about males who are shorter than their peers or who have delayed sexual development.[21] Other important endocrinological etiology was hypothyroidism, diagnosed in 12 (5.6%) cases of short stature in this study. Reported incidence in other studies is in the close range.[17,20]

On the other hand, the most common non-endocrinological causes were malnutrition (9.8%) and coeliac disease (6.5%), these results are consistent with many worldwide studies.[7] Utah growth study concluded that PEM and malabsorptive syndromes were responsible for 10% of short stature, whereas, it was 12.7% in another study from neighbouring country, India.[4,23] Though, Zargar *et al.* and Moayeri *et al.* reported the Road Traffic Accidents (RTA) as the most common non-endocrinological cause for short stature in their studies.[3,17] In this study, RTA contribution was only 1.9%. This may be due to lack of timely presentation or insufficient diagnostic workup in the local population. In this study, few rare cases of multiple growth abnormality syndrome were also diagnosed with presentation mainly of short stature and abnormal facies. Another striking difference was Turner syndrome, which was present only in 2 girls making only 2.7% in female patients contrary to much more frequent reporting in other studies.[26] This can be explained on the basis that chromosomal analysis was not done in every female child as the cost of investigation was quite high and secondly this facility was available only in few places. Another result was the rarity of psychosocial dwarfism and two such cases (both females from low socioeconomic families) were identified in 214 short statured children, which is contrary to other studies.[27] Child neglect may be the reason or the family social system may be a real bar for recognition of this condition.

Nevertheless, the most common cause of short stature was normal variants of growth as a group. CGD ranked as the commonest in males and FSS in female subjects; the same was concluded by Bhadada *et al.* in their study of 352 children with short stature in India.[4] Below 05 years of age, pathological short stature was 77.4% while above 05 years, it was 50.5% (p<0.05). Another important observation made in this study was that 79.2% of cases with pathological short stature were having height falling below 0.4th percentile on nine centile UK growth charts compared to normal variants, where only 20.8% cases were falling below 0.4th percentile (p<0.05). Most children whose height falls below the 3rd centile but not below 0.4th centile, were normal (60.7%), with only few having endocrine abnormalities.

CONCLUSION

CGD and FSS are the leading causes of short stature in children whereas, GHD is relatively less common with a predilection for males. Thus the GH axis should only be investigated in selective cases and after adequate monitoring of growth and exclusion of other causes of short stature. Children with height falling below 0.4th centile are more likely to have a pathological cause for their short stature (p < 0.05). Thus the use of UK growth charts with 9 percentile lines designed by Child Growth Foundation, UK, appears to be appropriate for use in our country. Short stature children under 05 years of age were more likely to have a pathological cause.

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