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Etiological Factors of Short Stature in Bangladeshi Children and Adolescents: Experience at a tertiary care hospital in Dhaka, Bangladesh

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Abstract:
Introduction: *Accurate anthropometric measurements and critical analysis of growth data allow the clinician to promptly recognize children with short stature. The aim of this study was to determine the frequency of etiological factors causing short stature among children referred to the Department of Pediatric Endocrinology and Metabolioc Disorder (outdoor unit), Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh.*
Material & Methods: *This was a cross sectional study which was conducted in the Department of Pediatric Endocrinology and Metabolioc Disorder (outdoor unit), Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh in the mentioned hospital were finalized as the study population. We conducted this descriptive observational study from Jan 2015 to Dec 2016, to analyze 106 children (boys 59, girls 47) with short stature. Evaluation included: detailed medical history, physical examination, laboratory tests, bone age and chromosomal analysis. Data was entered, coded, cleaned, and analyzed by using Statistical Package for Social Science (IBM SPSS), version 20.*
Results: *The major etiological causes of non-pathologic variants of short Stature accounted constitutional growth delay (CGD) was 65(61.3%) and had familial short stature (FSS) was 27(25.47%). WhereasEndocrinological causes accounted for 33(31.01%) of short stature [of them, 16(15.09%) had growth hormone deficiency (GHD) and Primary hypothyroidism12(11.32%)], 63(59.26%) had normal variants of growth [of them, 12(11.32%)had familial short stature (FSS), 28(26.4%) had constitutional growth delay (CGD) and 6.6% combination of both]. Interestingly, Turner's Syndrome (TS) constituted 10(9.4%) of children with short stature in our cohort.*
Conclusion: *Although potentially treatable causes such as GHD, hypothyroidism and TS accounted for a considerable percentage of short stature in our study, the majority of short stature in children had normal variations of growth. Growth hormone treatment in children, however, should be promptly initiated with specific clinical indications. TS is a not uncommon cause of short stature.*
Key Words: *Etiological Factors, Short Stature, Adolescent*

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I. Introduction

Short stature is one of the most common causes of referral to pediatric endocrinology clinics.1 Altered growth potential may result from disturbances of the endocrine system, altered nutrition or chronic diseases.2 Adult height is largely genetically predetermined, and height variations can be explained by genetic factors, although environmental factors also play a vital role. Short stature is a term applied to a child who is two standard deviations or more below the mean height for children of that gender and chronologic age (and ideally of the same racial ethnic group). This translates into being below the third percentile forheight.3 Short stature, although not a disease as per, is a manifestation of several diseases.4 The normal variant short stature does not need any medical or hormonal treatment, however, associated emotional stress should be addressed appropriately.5 While

literature is replete with studies on short stature, the relative significance of the different factors that affect growth velocity (genetic, perinatal, and local environmental factors) varies in different populations.6,7 To the best of the authors' knowledge, pattern of short stature in Bangladeshi children was not previously reported. The aim of this study was to determine the frequency of different causes of short stature in children and adolescents at the Department of Pediatric Endocrinology and Metabolioc Disorder (outdoor unit), Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh and to compare our results with previous studies.

II. Objectives

To determine the etiological factors of short stature in Bangladeshi children and adolescents.

III. Methodology And Materials

This was a cross sectional study which was conducted in the Department of Pediatric Endocrinology and Metabolioc Disorder (outdoor unit), Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh in the mentioned hospital were finalized as the study population. We conducted this descriptive observational study from Jan 2015 to December 2016. After discussion of details of the study with the children's legal guardians, an informed consent was taken from the parents/guardians. All patients were referred from different hospitals, clinics and Pediatrician all over Bangladesh to our Pediatric Endocrinology and Metabolioc Disorder (outdoor unit). Recruitment for the study was based on the following inclusion criteria: (1) age below 18 years; (2) height is two standard deviations or more below the mean (below 3rd percentile) according to the indian pediatrics growth chart which are standardized, based on WHO growth charts;(3) growth velocity < 4 cm/year, or small for the mid parental size; and (4) adequate follow up (for at least 6 months). The exclusion criteria were: (1) height is not –2SD or below 3rd percentile for age and sex with normal growth rate; (2) children on regular follow up for a known and documented chronic disease or debilitating disease; or (3) inadequate follow up. All patients were examined by pediatric endocrinologists. We followed the specific work-up protocol for short stature developed by the European Society for Pediatric Endocrinology.8 We did the following for all children: detailed history, family history of short stature, age at puberty of each parent, demographic profile, obtaining birth weight, and systemic physical examination. In addition, we measured the anthropometric profile of the patients and their parents; height was measured in centimeters by standard technique using a stadiometer and weight in kilograms using an electronic balance. Lower segment is the result of subtracting sitting height from standing height, then upper to lower segment ratio was calculated. 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 subject was measured with all the clothing removed except undergarments. Body mass index was calculated as weight (kg) divided by square of the height (m). Target height was calculated by the method of mid-parental height, the average of the mother's and father's height ± 6.5 cm (addition in boys or subtractions in girls).8 Stages of puberty in the 9–15-years' age group were determined according to the classification of Marshall and Tanner.9,10 The following primary screening tests were performed in all subjects: complete blood count, erythrocyte sedimentation rate, hepatic and renal function test, electrolytes, calcium, phosphorus and alkaline phosphatase that were performed by Cobas Integra 400 plus (Swiss, Serial number: 500558). Thyroid stimulating hormone (TSH), free thyroxine (FT4), serum cortisol, 24 h urinary cortisol, urinalysis, urine culture, abdominal ultrasound and bone age radiographs were also performed. Bone age was determined by two pediatric radiologists using published standards of Greulich and Pyle's atlas of skeletal development.11 After excluding other causes of short stature or systemic diseases in those children who had normal baseline investigations and a strong clinical suspicion of growth hormone deficiency (GHD) (height >3 TS below the mean with or without growth velocity < 4 cm/year or height 2 TS or more below the corrected mid-parental height, and delayed bone maturation),GH levels (after appropriate provocation test). GHD defined as peak serum level under 10 ng/l with low IGF-1.12,13 In patients with proven GHD by dynamic testing, magnetic resonance of the pituitary was performed. Children born small for gestational age and failing to achieve catch-up growth were investigated and subsequently, growth velocity was monitored to rule out other causes. Chromosomal study was performed in females with significant short stature (height <3 TS below the mean) and with unknown etiology, with or without other stigmata of Turner's syndrome. A diagnosis of idiopathic short stature was considered in children with short stature, a subnormal growth rate, delayed bone age, no apparent medical cause for growth failure, and normal growth hormone (GH) response to provocative testing.14 Skeletal dysplasia was con- firmed by skeletal surveys. Short stature children who present for the first time and had chronic diseases causing decreased

growth velocity were diagnosed on the basis of history, physical examination and relevant lab investigations.

Thyroid profile: TSH was estimated by immu- noradiometric assay (IRMA), while FT3 and FT4 were estimated by radioimmunoassay kits from Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh.

Stimulation of GH secretion by two provocation tests (clonidine test and insulin tolerance test) separated by a 1-week interval was done. GH was analyzed by IRMA. The dose of clonidine given before the test was 0.15 mg/m2 orally while that of insulin was 0.1 IU/kg intravenously. In the insulin tolerance test, the blood glucose should decrease by 50% or more of the basal value or decrease to 40 mg/dl. If no hypoglycemia occurred, another dose of insulin (0.05 IU/kg) was given. With adequate hypoglycemia, peak GH levels < 10 ng/ml indicated GHD. In Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh, we do the provocation tests by L-DOPA. L-DOPA are used in GH provocation tests which is done from BIRDEM Hospital Dhaka, Bangladesh.

Statistical analysis: Continuous variables were represented as means ± SD, and categorical variables were expressed as frequencies and percentages. The significance in difference of the continuous and categorical variables was evaluated by the independent t test and the chi-square test, respectively. We used descriptive statistics to show patients' demographic data and we used SPSS version (16.0) to compute statistical calculations. For the effective sample size and statistical power calculations we used the online tool 'Sample size calculator' from ClinCalc.com, developed by Sean P. Kane from Butler University, Indianapolis, USA. A statistical power of 80% was used to avoid false-negative associations, assuming a 5% type I error rate. Confounding variables like age and sex were controlled by stratification.

IV. Results

During the study period, we recruited a total of 106 children and adolescents (59 boys and 47girls, with a ratio of 1.25:1) with short stature. Their age ranged from 3 to 18 years, with mean age of 9.45 ± 3.7 years. At this sample size, the study has a power of 85%, a confidence level of 95% and alpha error of 5% assuming a known frequency of endocrinological short stature of 25%[5-7]and expected frequency of 20%, based on our preliminary results. The mean age in boyswas 9.6 ± 3.9 years with median age of 10 and interquartile age of 8 years, and in girls was 9.3±3.6 years with median age of 9 and interquartile age of 7 years. The majority (68%) of the children were between the ages of 7-12 years (Table 1). The major etiological causes of non-pathologic variants of short Stature accounted constitutional growth delay (CGD) was 65(61.3%) and had familial short stature (FSS) was 27(25.47%) in (Tab-2). Then Endocrinological causes of short stature accounted for 33(31.01%) of short stature [of them, 16(15.09%) had growth hormone deficiency (GHD) and Primary hypothyroidism 12(11.32%)] (Tab-3).Finally in the (Table-4) we found that the Systemic non-endocrinological causes of short stature accounted 73(70.9%) where constitutional growth delay (CGD) in 28(26.4%), familial short stature (FSS) in 12(11.32%), Turner's syndrome (TS) in 10(9.4%), Ranaltuberlar acidosis short stature in 6(5.66%),Skeletal dysplasia 5(4.71%),Hypophosphatemic rickets 4(3.77%).

Table 1: Age and sex distribution of children with short stature (n=106)

Age (years)	Males (n=59)	Females (n= 47)	Total (n=106)	
	n	n	n	%
3-6	10	5	15	14.15
7-12	36	32	68	63.21
13-18	13	10	23	22.64

Table2: Non-pathologicvariantsofshortstature (*n* =106)

Etiology	**N%**	**%**
CGD	65	61.3
FSS	27	25.47
FSS and CGD	7	6.6
Idiopathic short	4	3.77

stature		
Small for gestional age	3	2.83

Table 3: Endocrinological causes of short stature (*n* =33)

Etiology	**n**	**%**
GHD	16	15.09
Primary hypothyroidism	12	11.32
Congenitaladrena lhyperplasia	2	1.8
Cushing syndrome	2	1.8
Precociouspuberty	1	1

Table 4: Systemic non-endocrinological causes of short stature (n=73)

Etiology	**n**	**%**
Constitutional growth delay	28	26.4
Familial short ststure	12	11.32
Renal tubular acidosis	6	5.66
Skeletal dysplasia	5	4.71
Turner syndrome	10	9.4
Hypophosphatemic rickets	4	3.77
Juvenile rheumatoid arthritis	2	1.8
Crystic fibrosis	2	1.8
Osteogenesis imperfecta	2	1.8
Fanconi anemia	1	1
Children with unidentified genetic defects	1	1

V. Discussion

Short stature can be a sign of disease, disability, and social stigma causing psychological stress. It is important to have an early diagnosis and treatment. In this study, The major etiological causes of non-pathologic variants of short Stature accounted constitutional growth delay (CGD) was 65(61.3%) and had familial short stature (FSS) was 27(25.47%) .Then Endocrinological causes of short stature accounted for 33(31.01%) of short stature [of them, 16(15.09%) had growth hormone deficiency (GHD) and Primary hypothyroidism 12(11.32%)]. Furthermore, we found that the Systemic non-endocrinological causes of short stature accounted 73(70.9%) where constitutional growth delay (CGD) in 28(26.4%), familial short stature (FSS) in 12(11.32%), Turner's syndrome (TS) in 10(9.4%), Ranal tuberlar acidosis short stature in 6(5.66%), Skeletal dysplasia 5(4.71%),Hypophosphatemic rickets 4(3.77%). making it the leading cause of short stature in this study. Our finding regarding the dominance of normal variants of growth is in agreement with other recent studies in children with short stature.6,15-17 The hallmarks of genetic (familial) short stature include a bone age appropriate for chronologic age, normal growth velocity, and predicted adult height appropriate to the familial pattern. By contrast, CGD is characterized by delayed bone age normal growth velocity, and predicted adult height appropriate to the familial pattern. Patients with CGD typically have a first-degree or second- degree relative with CGD and late puberty.16 In this study, 12.26% of short stature children had nonendocrinological systemic causes of short stature compared with 26% with endocrinological causes. In fact, endocrine diseases are generally rare causes of short stature, and their contribution to short stature, particularly in children, varied markedly in different studies, ranging from 5% up to 35%.15,17,18Furthermore, GHD in our cases constituted 44.5% of the endocrinological causes and 11.7% of the short stature children and adolescents. These findings are in agreement with Lashari et al.,17 who reported a similar frequency of GHD in a clinic-based study. The prevalence of GHD in children with short stature varied markedly and ranges from 2.8% to 69%.18,19 Some other studies, like a study from India, reported quite a higher frequency (23.4%) of GHD in their children.6 Most of these studies, however, were conducted in endocrine referral centers, where the prevalence of endocrine disorders, especially GHD, is more likely to be of higher frequency. Moreover, some of these studies were underpowered due to the small number of children recruited and the reported frequencies may not reflect the true frequency of GHD in the community.15 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 the cut-off serum concentration in two consecutive provocative tests.12 There is no worldwide consensus on the definition of GHD but most pediatric endocrinologists use a cut-off serum GH concentration of 10 ng/ ml (10 ug/l or 904 pmol/l).20 Thus, from a clinical point of view: (1) in the general population, most children with short stature will not have GHD, and therefore, caution should be used when a clinician is interpreting the results of GH testing (the specificity and sensitivity of any tests of GH secretion is only 80%). Thus, the clinicians should

expect false-positive and false- negative results and hence, the therapeutic decision should not be based solely on GH tests; (2) velocity is the most critical factor in evaluating the growth of a child, therefore anthropometric measurement (height and weight) should be carefully measured and plotted accurately on growth charts. The final decision of GH therapy should be based on careful observation of growth, and calculation of growth rate at an interval of not less than 6 months or preferably.

VI. Limitations Of The Study

This was a prospective type of study in a single community with comparatively small number of sample size. So, the study result may not reflect the exact scenarios of the whole country.

VII. Conclusion And Recommendations

Although GHD, hypothyroidism, TS and other potentially treatable causes accounted for a con siderable percentage of short stature, the majority of children had normal variations of growth. GH treatment should be promptly initiated with specific clinical indications. TS is a not uncommon cause of short stature. Larger scale, community based studies would better describe short stature in particular populations.

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