Original Paper

Pattern and Frequency of Short Stature in Albanian Children

AGIM GJIKOPULLI[1], LINDITA GRIMCI[1], LAURANT KOLLCAKU[1], PASKAL CULLUFI[2], AFERDITA TAKO[3]

[1]Division of Pediatric Endocrinology, Department of Pediatrics, University Hospital Centre "Mother Teresa", Albania
[2]Division of Pediatric Gastro-enterology, Department of Pediatrics, University Hospital Centre "Mother Teresa", Albania
[3]Division of Pediatric Neurology, Department of Pediatrics, University Hospital Centre "Mother Teresa", Albania

ABSTRACT: Introduction:Short stature is defined as a standing height more than 2 standard deviations (SDs) below the mean for age and sex. While there are many medical causes for being short and having poor growth, including growth hormone deficiency, hypothyroidism, Turner syndrome, inflammatory bowel disease, kidney problems, malnutrition, etc., most children who are short are normal. Objectives: The identification and analysis of causes and factors leading to short stature in Albanian children. Patients & methods: Subjects enrolled in our study were admission with "Short stature" or "Slow growth velocity" from January 2001 to January 2011 and met the criteria: length < -2 z- score and/or height velocity <-2 z- score for age and sex. They were evaluated by anthropometric measurements; biochemical panel; hormonal balance; radiological studies; and hormonal provocative tests. Statistical processing was done with Epi-Info CDC 2000 and SPSS accordingly. Results: The age of the 564 children was from 0.65-18.74 years (11.08 ± 3.28 years). M / F: 221/343 (39% /61%) respectively. The frequency of diagnoses resulted as follows: the "constitutional short stature" 211children (37.4%), "GH deficit" 155(27.5%), "genetic syndrome" 67(11.9%), "familiar short stature" 38(6.7%), "others pathology" 38(6.7%), "idiopathic short stature" 31(5.5%), "i-uterine short stature" 16(2.8%). Conclusions:The fact that 46% of the explored children resulted positive in terms of a pathology that had caused primary or secondary growth failure, makes it necessity careful monitoring of growth and reference of the children to a specialist as fast as possible. Evidently great age of exploration indicates a weak surveillance on growth monitoring in Albania. Recommendations: Assessment of the child's growth must be a routine procedure. The early identification of stature growth delay will significantly increase the early detection of any pathology.

KEYWORDS: *short stature, HAZ (heigh for age z-score).*

Introduction

Growth is an important objective parameter of general health of a child. Short stature is a common problem encountered by practicing pediatricians, especially in developing countries. It results from an intricate process which involves integration of genetic potential, function of the endocrine system, nutritional status, effects of chronic diseases, and physical activity level. A disturbance at any point of these levels may affect growth adversely resulting in short stature [1] which is defined as a height of less than 3rd percentile or 2 standard deviations below the mean height for age and sex in the same ethnic group. 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) [2, 3, 4]. These are variants of normal growth and need no medical treatment; however, emotional stress associated with it should be alleviated [5]. Almost every chronic disease can cause short stature such as renal disease, malignancy, pulmonary disease, Cystic Fibrosis, cardiac disease etc. Coeliac disease is a prime example of a remediable cause of short stature, especially in younger children [6]. Nutritional deprivation and therapies like glucocorticoids, chemotherapeutic drugs, and radiotherapy can result in short stature [7]. Common endocrinological causes of short stature include hypothyroidism, hypopituitarism (isolated GHD or multiple anterior pituitary hormone deficiencies), hypercorticism and classical Laron syndrome [8, 9]. 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 [10, 11].

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

Methodology

This is a register based cohort study over a period of 10 years from January 2001 to January 2011 in the Pediatric Endocrine Unit,

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Department of Pediatrics, University Hospital Centre "Mother Teresa", Albania. All children were resident in Albania.

Included criteria were: age below 19 years, height more than 2 SD below the mean (< 3rd percentile), slowly growing with poor height velocity for age [less than 6cm/year (for patients ≤ 3 years old) and less than 4cm/year (for patients > 3 years old)] and a delayed bone age (more than 2 years), or small for midparental height and adequate follow-up (at least for 6 months). Excluded criteria were known diagnosed like 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 database. Standing height without head or foot gear (measured with a stadiometer), upper to lower segment ratio, weight and head circumference were measured. For children less than 2 years old was perform length 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. Height of patients were plotted using the WHO growth charts (Anthro and Anthro_plus 2007) and were standardized by calculating their height z-score [12]. Stages of puberty were determined according to the classification of Marshall and Tanner. Onset of puberty was defined by achievement of

testicular volume of 4 ml or more in boys or breast stage 2 in girls [13]. Bone age was determined in all cases by radiological assessment (by a single observer) of the epiphyseal maturation or shapes of bones of the left hand/wrist, comparing with Greulich-Pyle charts [14].

Mid parental height (MPH) was defined by using Tanner's method [15]. Mid parental height for boys (cm) = (father's height + mother's height + 13)/2; mid parental height for girls (cm) = (father's height + mother's height - 13)/2. Target height range = mid parental height +/- 6.5cm. Screening investigations included complete blood count, ESR, renal and thyroid function tests, glucose, calcium, phosphate, alkaline phosphatase, alanine aminotransferase and urinalysis.

In every case, at least 6 months of growth monitoring was done. Frequencies of various causes were analyzed in general and in three age groups (under 5 years of age; 5-10 years of ages and more than 10 years of ages). 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), FSS (i.e. proportionate short stature with a normal growth velocity, normal bone age, and short midparental height)[16] and Idiopathic Short Stature (ISS) when no causative disorder can be identified[17] (short stature, low growth velocity, without any apparent medical cause and normal growth hormone response to provocative testing). Non-endocrine systemic disorders were diagnosed by history, examination and appropriately selected laboratory tests. 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 10ug/L with two back to back provocative tests (Glucagon and Propranolol)[19]. Growth hormone level was measured by the ICMA in our center. Prepubertal children were primed with sex steroid before the growth hormone stimulation test. For all children who results with Growth Hormone Deficiency brain imagery was performed. Children born SGA and failing to achieve catch-up growth were investigated and subsequently growth velocity was monitored to rule out other causes. Genetic consult was asked for every child with dysmorphologic features. Karyotyping was carried out in those female subjects where

the etiology was in doubt, to rule out Turner's syndrome.

Results were expressed as mean ± standard deviation (SD). Data was analyzed using the IMB®SPSS® Statistics Version20. Pearson correlation analysis was performed on the data in order to analyze the relationship between various parameters with final height SDS. A p-value < 0.05 was considered as statistically significant.

Results

A total of 564 cases [343 males (60.8%), and 221 females (39.2%)] were identified as having short stature, with mean chronological age of 10.25±3.9 years, mean bone age of 7.65±3.01 years and mean height of age 7.58±2.63years. The difference between mean chronological age and bone age was statistically significant (p-value 0.001). Among the study population, mean mid-parents height was 160.42±10.14cm

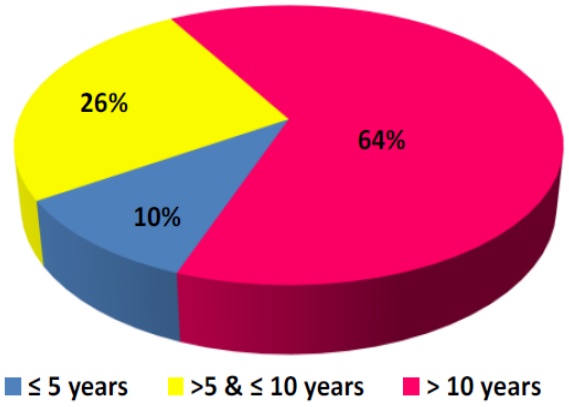

Fig.1. Age raport rate in population with short stature

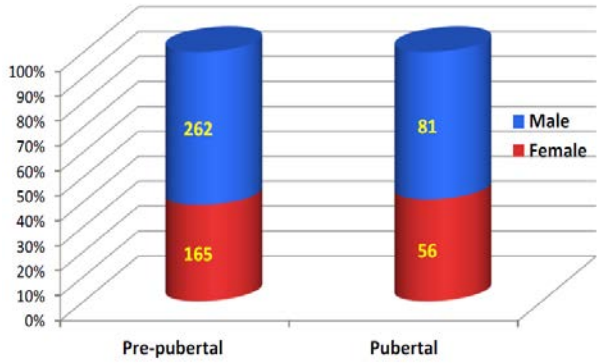

Fig.2.Raports based on pubertal stage in population with short stature

10% of total study population were on group-age under 5 years old; 26% were on group age more than 5 and less than 10 years old, and 64% were on group-age more than 10 years old (Fig.1). The difference in frequencies based on groups of age was statistically significant (p-value 0.002).

A total 427 (76%) of children were pre-pubertal and 137 (24%) were in pubertal stage. Male/female ratio based on pubertal stage was almost equal (Fig.2).

Height for age z-score (HAZ) for all children was -3.43±0.95 (HAZ for males was -3.44±0.89 and -3.41±1.04for females) p-value 0.823. (Fig.3 and Fig.4).

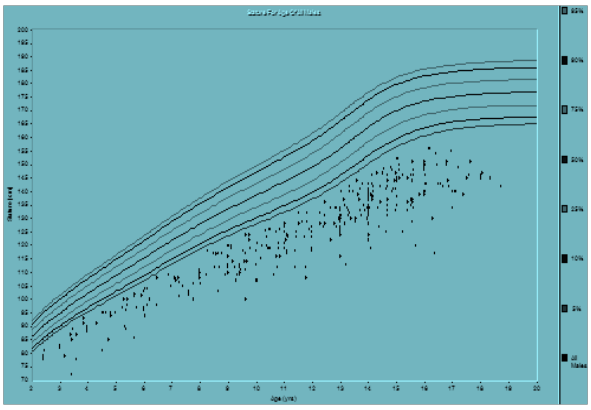

Fig.3. HAZ-score for all males

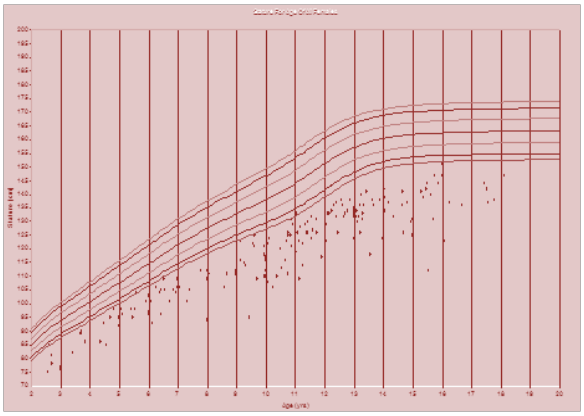

Fig.4. HAZ-score for all females

The frequencies of various causes of short stature in this study are shown in Table I. Two main etiological groups were identified:

Group of short stature with normal variant of growth with 280 (49.6%) children, where were included in three subgroups: Constitutional growth delay (CGD) 211(37.4%); Familial short stature (FSS) 38 (6.7%) and Idiopathic short stature (ISS) 31 (5.5%).

Group of short stature with pathologic variant of growth with 284 (50.4%) children, where were included also in two main subgroups: short stature with endocrinological cause 163(28.9%) and short stature caused by non endocrinologic disease 121(21.4%).

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Table 1: Causes of short stature (n=564).

Etiology	Total n (%)	Male n (%)	Female n (%)
A. Normal variants of growth			
Constitutional growth delay (CGD)	211(37.4%)	137(24.3%)	74(13.1%)
Familial short stature (FSS)	38(6.7%)	17(3.0%)	21(3.7**%**)
Idiopathic short stature (ISS)	31(5.5%)	16(2.8%)	15(2.7%)
B. Pathologic variants of growth			
a) Endocrinological causes			
Growth hormone deficiency (GDH)	155(27.5%)	115(20.4%)	40(7.1%)
Hypothyroidism	8(1.4%)	4(0.07%)	4(0.07%)
b) Non-Endocrinological causes			
Celiac disease	11(1.9%)	06(1.1%)	05(0.8%)
Genetic syndromes	75(13.3%)	34(6.0%)	41(7.3%)
Skeletal dysplasia	8(1.4%)	1(0.2%)	7(1.2%)
IUGR/SGA	16(2.8%)	9(1.6%)	7(1.2%)
Chronic anemia	2(0.35%)	1(0.18%)	1(0.18%)
Renal tubular acidosis (RTA)	2(0.35%)	1(0.18%)	1(0.18%)
Psychosocial dwarfism	4(0.7%)	1(0.18%)	3(75)
Neurofibromatosis	2(0.35%)	1(0.18%)	1(0.18%)
Hystiocytosis	1(0.18%)	00 (0%)	1(0.18%)
Total	564 (100%)	343 (100%)	221 (100%)

As shown on table 1 the main cause of short stature was CGD with 211(37.4%) children. Male/ female ratio was 1.8.

In endocrinologic cause of short stature, Growth hormone deficiency was find on 155(27.5%) children and thyroid hypofunction on 8(1.4%) children.

Genetic syndromes were the leading non endocrinologic causes of pathologic short stature with 75(13.3%) chilred. Turner syndrome was the most frequent with 24 girls (32%) of total syndromic children, followed by Noonan syndrome with 15 children (20%) of syndromic children.

In males, 49.6% were normal variants of growth, 15.7% had non-endocrinological diseases, while 34.7% had endocrinological diseases whereas, in females these values were 49.8%, 30.3%, and 19.9% respectively.

In this study, the five most common single etiological factors were CGD (37.4%), GDH (27.5%), FSS (6.7%), ISS(5.5%) and IUGR/SGA (2.8%) as shown in Table 1.

Discussion

Short stature has been studied extensively worldwide but, it's the first time in Albania. 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 [20]. Fortunately, majority of children with height falling below 3rd centile are part of normal population, with only a small number having endocrine abnormalities [21, 22]. Shuet al. have documented in their studies that normal variants may comprise as much as 65% of the short children [21]. In this study, the most common single etiology of short stature found was CGD, especially in boys. As a group, normal variants of growth, CGD, was responsible for 37.4% 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 [22]. 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 expert's radiological opinion. Timely identification of such cases not only helps to avoid extensive and unnecessary investigations but also alleviates parental anxiety. In this study, 50.4% of short stature children had pathologic variant of growth. Endocrinological causes contributed by 57.4%, while nonendocrinologic causes were 42.6% of all pathological variant of growth. Out of those, 27.5% were previously unrecognized for GHD, almost same as reported by Lebl J et al (29%) in Czech population[23] and in Virginia-USA as 23%[24], It must be noted that this study was conducted in the endocrine referral centers;

therefore, the prevalence of endocrine disorders, especially GHD, is bound to be high.

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, GHD was more common in boys, which is in accordance to a study from Iran [16]. 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[26]. Other important endocrinological etiology was hypothyroidism, diagnosed in 08(1.4%) cases of short stature in this study. On the other hand, the most common nonendocrinological causes were IUGR/SGA (2.8%) and coeliac disease (1.9%), but these results are lower with many worldwide studies [6].

A consideration grup presentation with short stature and dysmorphologic features was the sindromic group (13.3%). Turner syndrome was the most frequent (32%), followed by Noonan syndrome (20%) of all syndomic pathology.

Conclusion

CGD is 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 -3 z-score are more likely to have a pathological cause for their short stature ($p < 0.05$). Thus the use, of WHO growth charts, appears to be appropriate for use in our country.

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Corresponding Author: Agim Gjikopulli, Pediatrician at Division of Pediatric Endocrinology, Department of Pediatrics, University Hospital Centre "Mother Teresa", Albania, Qendra Spitalore Universitare "Nënë Tereza", Rruga e Dibrës 372, Tirana, Albania. Phone:0035542349209; e-mail: agimgjikopulli@yahoo.com