Suez Canal University Medical Journal Vol. 26 (12), 2023
Pages 1-11

Assessment of Causes of Short Stature in Children Attending Suez Canal University Hospital

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Abstract

Background: **Short stature is one of the most common referral causes to endocrinology pediatrics clinics. It is defined as a child with two standard deviations or more below the mean height for children of the same gender and chronological age. It occurs in about one in every 25,000–30,000 persons worldwide. Although short stature is not a disease, it may be a symptom of many diseases. So early detection allows the best chance for appropriate management.** ***Aim:*** **To describe the most common etiological factors of short stature in children attending Suez Canal University Hospital.** ***Patients and Methods:*** **This is a descriptive cross-sectional study involving all children attending the pediatric clinic or admitted inpatients whose age (2 -15) years old complained of short stature or were accidentally discovered to be short in the routine general examination.** ***Results:*** **A sample of 264 children complain of short stature. There were 26 (9.8%) participants with non-pathological short stature; 24 had familial short stature and 2 had constitutional short stature. There were 238 (90.2%) had pathological short stature; among them, 30 had nutritional diseases, 68 idiopathic, 125 endocrinal diseases (85 growth hormone deficiency, 16 hypothyroidism, 3 Addison, 5 rickets, and 16 diabetic), 2 had turner syndrome, and 13 had chronic diseases; (3 myelodysplastic syndrome, 3ulcerative colitis, 1 thalassemia, 4 celiac and 2 chronic chest disease (asthma).** ***Conclusions:*** **pathological short stature was more common than non-pathological causes. The most common cause of short stature was Growth hormone deficiency**

Keywords: growth failure, growth hormone, dwarfism

Introduction

Normal growth and development results from a complicated procedure that includes diet, active endocrine system, chronic disease effects, hereditary potential, and physical activity. Any disruption of any part of this procedure might disturb growth negatively in different ways, including short stature[1]. It is one of the most common referral causes to endocrinology pediatrics clinics[2]. It is defined as a child with two standard deviations or more below the mean height for children of the same gender and chronologic age (preferably of the same ethnic-racial group). This means below the third percentile for height[3]. Short stature is either

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proportionate (the upper segment/lower segment is normal for age, and height equals span) or disproportionate (the upper segment/lower segment is abnormal for age, and height doesn't equal span). The most common skeletal dysplasia is achondroplasia, which causes significant short stature (dwarfism)[4]. Achondroplasia has a milder form called hypochondroplasia. Both result from a genetic mutation. It is difficult to distinguish between achondroplasia and familial short stature. Other genetic conditions, such as Prader Willi syndrome, turner syndrome, or Down syndrome are also related to disproportionate short stature[5]. In children less than two years old the most common causes of proportionate short stature are familial short stature and constitutional short stature, which are non-pathologic, normal variants of development. Although short stature is not a disease in itself, it may be a symptom of many diseases[6]. Although 2.5 % of the population is short by definition, short stature occurs in about one in every 25,000–30,000 persons. Worldwide That means about 250,000 affected persons[7]. However, the number of children with growth failure is higher, due to the incidence of chronic diseases in childhood. The Utah Growth Study is the biggest population-based survey of growth in children assessed growth velocity and height in about 115,000 American children; among the 555 children with short stature and deficient growth rate (defined as growth velocity < 5 cm annually), five percent only had endocrinal cause of short stature. Also, 48% of the children with Turner syndrome or growth hormone deficiency in this big study had been untreated or undiagnosed. Most parents relate their children's primary cause of short stature to endocrine disorder (e.g., growth hormone disorder). The Utah Growth Study revealed that about 95%children with deficient growth do not have an endocrine disorder[8]. Short stature due to normal variations does not need any hormonal or medical treatment; but, the associated psychological impact should be handled properly[9]. The goal of evaluating a child with short stature is to detect the children with pathological causes of short stature (such as growth hormone deficiency, underlying systemic diseases, or Turner syndrome). It is also to assess the severity of the short stature and probable growth pattern for proper management[10]. Early detection of abnormal growth patterns and referral to the proper specialist allow children with short stature and/or growth failure the best chance for appropriate management and improved prognosis[11]. The primary evaluation of short stature should contain medical history, systemic physical examination, Anthropometric profile of the child and his parents, and determination of growth velocity, and bone age[12]. While there are many studies on short stature, the growth velocity is affected by many factors (e.g., genetic, perinatal, and local environmental factors), and their significance varies with different populations[13]. In Egypt, many studies assessed the prevalence and pattern of short stature. One study evaluated the causes of short stature among children in Assiut University Children's Hospital and revealed that 26% of short stature was due to endocrinal causes. Out of them, 63.6% had normal variants of growth (42% familial short stature, 15.8%constitutional short stature, and 5.5% a combination of both) and 11.8% had growth hormone deficiency. Interestingly in this study celiac disease represented 6.6% of children with short stature[14]. Another study held in Menoufia revealed that total short stature represented 17%. The main causes of short stature were familial (40.8%) and constitu-

tional (24.2%). Twenty-six percent of those children were diagnosed with anemia, while anemia with stunting was reported in 9.9% and both are most common among girls (30.0% and 11.4%, respectively)[15]. This study aims to describe the most common etiological factors of short stature in children attending Suez Canal University Hospital.

Subjects and Methods

We performed a descriptive cross-sectional study among inpatient and outpatient pediatric clinics at Suez Canal University Hospital. The study involved 264 children who attended a pediatric clinic or were admitted to the inpatient whose age (2-15) years complained of short stature or were accidentally discovered to be short in the routine general examination. According to standard WHO growth charts, short stature is defined as a Height of two standard deviations or more below the mean (below the 3rd percentile)[16]. We assessed all children for

Medical history
Perinatal history for exposures; infection, drugs, radiation. Birth weight and length (to differentiate between prenatal and postnatal causes). difficulties e.g., microphallus, poor suckling& hypoglycemia in hypopituitarism. Family history for short stature, parent's pubertal age, short siblings, demographic profile, and social problems. history suggestive of chronic systemic diseases such as a history of chronic diarrhea in malabsorption syndrome, chronic hemolytic anemia, chronic renal failure or UTI, chronic heart and chronic chest diseases. Endocrinal disorders e.g., Hypothyroidism, hypopituitarism, diabetes mellitus, hypercortisolism, precocious puberty, and diabetes insipidus

The Paediatric Yorkhill Malnutrition Score (PYMS): For detecting malnutrition, it is a simple structured questionnaire consisting of four parameters that assess and predict the signs and symptoms of malnutrition, and many studies have assessed its diagnostic accuracy[17].

Complete Systemic physical examination: for nutritional state assessment check muscle wasting, and signs of vitamin deficiencies (e.g., brittle hair and nail, dry skin, and mouth ulcers). Complete systemic examination: including cardiac, chest, abdomen, and neurological examination. Also examine for features and signs suggesting endocrinal disorders like a large protruding tongue, and short neck in hypothyroidism. Check for dysmorphic features e.g., female with wide-spaced nipples and neck webbing in Turner syndrome.

Anthropometric profile of the children and their parents: weight, height, arm span, upper segment to lower segment ratio, and arm span to height ratio to differentiate between proportionate and disproportionate short stature using CDC growth charts for boys and girls aged 2-20 years old (height-for-age, weight-for-age). The American Academy of Pediatrics and the CDC recommend using the 2006 World Health Organization growth charts for children between birth and age 2 years and the 2000 CDC standard growth charts for children aged 2 to 20. By entering growth measurement inputs into both growth charts, medical providers can obtain growth percentiles and z-scores (this process is automated in many electronic health record systems).

A) The classification of Marshall and Tanner to assess secondary sex features of children during puberty[18].

B) Primary screening tests i.e., Complete blood count, liver function tests, ESR, kidney function tests, thyroid profile, stool analysis, urine analysis, serum electrolytes[19]& bone age radiographs. *C) Growth hormone level* in children with normal primary investigations but still have high clinical suspicion of growth hormone deficiency. *D) Pelvic-abdominal ultrasound* for all girls with short stature to the primary exclusion of Turner's syndrome. *E) Chromosomal Karyotype* In all girls with unexplained short stature to rule out Turner syndrome. *F) Echocardiography* for suspected cardiac defect

Constitutional delay of growth and puberty is a growth pattern characterized by a normal size at birth and subsequent slowing of height velocity in the first 3 to 5 years of age. Individuals then maintain a prepubertal growth velocity during the expected time of pubertal growth spurt, resulting in a markedly decreased height percentile (can be below the 5th percentile), especially in early adolescence. The hallmark in diagnosis is a delayed bone age finding[20].

Familial short stature (FSS) is considered a normal variant, where a child's height is less than 2 SDs for his age, but the child's height is expected to still reach the calculated mid-parental height. These children have low normal height velocities, a normal laboratory evaluation finding, and a bone age that agrees with his or her chronological age. FSS is generally considered a subset of idiopathic short stature (ISS). It is worth noting that a diagnosis of FSS does not preclude underlying monogenic or polygenic alterations, as multiple family members may carry genetic variants responsible for short stature[21].

Idiopathic short stature is a heterogeneous diagnosis of exclusion, which is, by definition, stature 2 SDs below the mean for age, gender, and population, with normal size for gestational age at birth, absence of chronic disease, endocrine deficiency, or chromosomal abnormalities; and normal nutritional status[21].

Growth hormone deficiency should be suspected in children who have a below-average growth rate, crossing height percentiles, and have a delayed bone age finding[22]. In children, initial laboratory testing for GH deficiency includes measurement of serum IGF-1 and IGF-1 binding protein 3 (IGF-BP3) levels. GH is secreted in a pulsatile manner; thus, single measurements are non-diagnostic for GH deficiency. If IGF-1 levels are low for age and pubertal status or there is high clinical suspicion, a GH stimulation test should be performed[23].

Results

Two hundred sixty-four children were enrolled in this study; there were 126 (47.7%) males and 138 (52.3%) females. 9.8% of the participants had non-pathological short stature, 9.1% had familial short stature, and 0.7% had constitutional short stature. While 90.2% of the participants had pathological short stature with 11.4% had nutritional causes, 25.8% had idiopathic short stature, 47.3% had endocrinal reasons (1.1% Addison disease, 1.9% rickets, 6.1% diabetes mellitus, 32.2% growth hormone deficiency and 6.1% had Hypothyroidism.), 0.8% had turner syndrome, and 4.9% had chronic systemic diseases (1.1% myelodysplastic syndrome, 1.1% ulcerative colitis, 0.4% thalassemia, 1.5% celiac disease and 0.8% chronic chest disease (Asthma)) (Table 1).

Table 1. Causes of short stature among the participants (n = 264)		
Causes	**No.**	%
Non-pathological	**26**	**9.8**
Familial	**24**	**9.1**
Constitutional	**2**	**0.7**
Pathological	**238**	**90.2**
Nutritional	**30**	**11.4**
Idiopathic	**68**	**25.8**
Turner syndrome	**2**	**0.8**
Endocrinal	**125**	**47.3**
• Addison	3	1.1
• Rickets	5	1.9
• Diabetes mellitus (DM) type 1	16	6.1
• Growth hormone deficiency	85	32.2
• Hypothyroidism	16	6.1
Chronic systemic diseases	**13**	**4.9**
• Myelodysplastic syndrome	3	1.1
• Ulcerative colitis	3	1.1
• Thalassemia	1	0.4
• Celiac	4	1.5
• Chronic chest disease (Asthma)	2	0.8

Regarding the different parameters of the laboratory findings among the participants, 92.8% showed normal Hb while 7.2 were anemic. 98.1% had an average PLTs count, while 1.1% had thrombocytosis and 0.8% had thrombocytopenia. Regarding the leukocyte count, 97.7% had normal leukocytic count, 1.1% had leukopenia, and 1.1% had leukocytosis. Regarding the tanner stage of the participants in our study, 64.4% had a normal tanner stage for age, while 35.6% had an abnormal tanner stage (low for age). In an assessment of bone age, 43.2% of the participants had delayed bone age, while 56.8% had normal bone age. Also, 68.2% of the participants had no parents' consanguinity, while 31.8% had positive parents' consanguinity. Almost ninety-eight percent of the participants had no NICU admission, while 1.9% were admitted to NICU. Almost thirty-five percent of the participants were delivered by cesarean, while 64.8% had a normal vaginal delivery. Also, 92.8% of the participants had normal birth weights, while 7.2% had low birth weights. Regarding the pediatric Yorkhill malnutrition score (PYMS) there were 85.6% had normal nutritional status while 14.4% had affected nutritional status. There was no statistically significant association between PYMS as a reflection of the nutritional status and iron deficiency anemia among participants. Also, there was no statistically significant association between PYMS as a reflection of the nutritional status of the participants and rickets or diabetes mellitus. At the same time, there was a statistically significant association between participants with chronic systemic diseases and PYMS as a reflection of their nutritional status (Table 2). Participants had no statistically significant association between parents' consanguinity and familial causes of short stature.

Table 2: Relation between PYMS and (Rickets, Iron deficiency anemia, diabetes mellitus, chronic systemic diseases) (n = 264)						
	PYMS					
	Normal (n = 226)		Affected (n = 38)		χ^2	^{FE}p
	No.	%	No.	%		
Rickets						
No	221	97.8	38	100.0	0.857	1.000
yes	5	2.2	0	0		
Iron deficiency anemia						
sufficient	223	98.7	37	97.4	0.371	0.465
deficient	3	1.3	1	2.6		
Diabetes mellitus						
Not diabetic	210	92.9	37	97.4	1.068	0.481
diabetic	16	7.1	1	2.6		
Chronic systemic diseases						
Yes	7	3.1	6	15.8	11.193*	0.005*
No	219	96.9	32	84.2		

*χ^2:Chi square test, FE: Fisher Exact, *: Statistically significant at p ≤ 0.05*
p: p-value for comparing between Normal and Affected

There was a statistically significant relation between idiopathic short stature and gender; females are more susceptible to idiopathic short stature. Also, the participants had a statistically significant association between Idiopathic short stature and tanner stage. There is no statistically significant relation between idiopathic short size among the participants and parents' consanguinity (Table 3).

Table 3: Relation between Idiopathic causes of short stature with gender, parent's consanguinity, and tanner stage						
	Idiopathic					
	No (n = 196)		Yes (n = 68)		χ^2	p
	No.	%	No.	%		
Gender						
Male	101	51.5	25	36.8	4.412*	0.036*
female	95	48.5	43	63.2		
Consanguinity						
No	129	65.8	51	75.0	1.963	0.161
yes	67	34.2	17	25		
Tanner stage						
Normal for age	106	54.1	64	94.1	35.293*	<0.001*
Abnormal (low for age)	90	45.9	4	5.9		

χ^2:Chi square test: Statistically significant at p ≤ 0.05*

There was a statistically significant relationship between growth hormone deficiency among the participants and parents' consanguinity, Hypothyroidism, gender, birth weight, tanner stage, bone age, and NICU admission. Almost fifty-four percent of growth hormone deficiency patients have no parents' consanguinity,

while all participants with GHD had no hypothyroidism. Males are more susceptible to GHD than females. Almost all participants with GHD had normal birth weight, while most had low for age tanner stage. Nearly all participants with GHD had delayed bone age, while most had no NICU admission (Table 4).

Table 4: Relation between growth hormone deficiency with parents' consanguinity, Hypothyroidism, gender, birth weight, tanner stage, bone age, and NICU admission

	Growth hormone deficiency					
	No (n = 179)		Yes (n = 85)		χ^2	p
	No.	%	No.	%		
Consanguinity						
No	134	74.9	46	54.1	11.430*	0.001*
yes	45	25.1	39	45.9		
Hypothyroidism						
No	163	91.1	85	100.0	8.088*	0.004*
yes	16	8.9	0	0		
Gender						
Male	74	41.3	52	61.2	9.089*	0.003*
female	105	58.7	33	38.8		
Birth weight						
Normal	161	89.9	84	98.8	6.803*	0.009*
Low birth weight	18	10.1	1	1.2		
Tanner stage						
Normal for age	148	82.7	22	25.9	81.093*	<0.001*
Abnormal (low for age)	31	17.3	63	74.1		
Bone age						
Delayed	30	16.8	84	98.8	158.191	<0.001*
normal	149	83.2	1	1.2		
NICU admission						
No	178	99.4	81	95.3	5.335	0.038*
yes	1	0.6	4	4.7		

χ^2:Chi square test: Statistically significant at p ≤ 0.05, **p:** p-value for comparing between No and Yes*

Discussion

Growth is an accurately regulated procedure and is a vital intrinsic component of childhood health. The linear growth procedure can be predisposed by genetics significantly, but final adult height is affected by external factors, such as environmental factors, hormonal, and nutritional[1,13]. Short stature is defined as height two or more standard deviations (SD) below the mean for children of the same sex, age, and ethnic-racial group which means below the third percentile[3]. Short stature in children may be due to normal growth variations or pathological causes. Close monitoring and assessment of growth in children are important for the early detection of pathological treatable causes versus normal growth variations[11]. There is no accurate data for the prevalence of short stature in developing countries. Factors involved in the pathogenesis of short stature in developing countries vary from developed countries due to the differences in race, lifestyle, nutritional, and socioeconomic factors. Short stature is among the most common

causes of referral to pediatric endocrinology clinics. Different growth potential may be due to endocrine system disorders, malnutrition, or chronic diseases[2]. This descriptive cross-sectional study involved 264 children attending the pediatric clinic or admitting in the inpatient whose age (2 -15) years old complained of short stature or were accidentally discovered to be short in the routine general examination. This study aimed to improve child health through the early identification, detection, and management of pathological causes of growth failure. The main objectives were to describe the most common etiological factors of short stature in children attending Suez Canal university hospital. In this study, 9.8% of the participants had non-pathological short stature, 9.1% had familial short stature, and 0.8% had constitutional short stature. While 90.2% of the participants had pathological short stature, among them, 11.4% had nutritional causes, 25.8% had idiopathic short stature, 47.3% had endocrinal reasons (1.1% had Addison disease, 1.9% had rickets, 6.1% had diabetes mellitus, 32.2% had growth hormone deficiency (GHD) and 6.1% had Hypothyroidism), 4.9% had chronic systemic diseases (1.1% had myelodysplastic syndrome, 1.1% had ulcerative colitis, 0.4% had thalassemia, 1.5% had celiac disease, and 0.8% had chronic chest disease (Asthma)) and 0.8% had turner syndrome. The most common endocrinal cause of short stature is growth hormone deficiency, and the most common chronic disease that causes short stature is celiac in this study. In agreement with our results, Song et al[24] showed that the most common pathological cause of short stature was growth hormone deficiency by 38.9%, followed by idiopathic short stature by 23.2%, small for gestational age by 11.3%, then Turner syndrome by 9.3%. The rest 12.4% had other causes, such as skeletal dysplasia, clinically defined syndromes, metabolic disorders, and chronic renal failures. GHD was diagnosed in about 20% of children with short stature. In agreement with our results, a Jordanian study by Zayed et al.[25]clarified that the most common cause of short stature among referred short children in Jordan was GHD by 69·1% and that prevalence was exceptionally high. In a study conducted in Egypt by El-Shafie et al.[15]identified the cause of short stature as; non-pathological causes such as familial by 40.8%& constitutional by 24.2%, and pathological causes such as idiopathic by 6.6%, malnutrition by 6.8%, endocrinal causes [Hypothyroidism (7.6%), GHD (9.7%)], non-endocrinal causes [celiac disease (3.4%), chronic kidney disease (0.5%)] and Turner Syndrome by 0.3%. In agreement with our results, the most common endocrinal cause of short stature is GHD, and the most common chronic disease that causes short stature is celiac. In Egypt, a study conducted by Hussein et al[14] found that the most common cause of short stature was the normal growth variants by 61.6% among them 37.5% Familial short stature, 15.8 % Constitutional growth delay , 4.5% having both familial and constitutional, 2% small for gestational age and 1.7% idiopathic short stature. There was a statistically significant association between idiopathic short stature and gender. Females are more susceptible to Idiopathic short stature. Also, the participants had a statistically significant association between idiopathic short stature and tanner stage. There is no statistically significant relation between idiopathic short stature among the participants and parents' consanguinity. This goes in line with another study by Rosenbloom[26] concluded that idiopathic short stature is a diagnosis of exclusion and needs to differ from Constitutional growth delay and

Familial short stature. The most frequent referral to pediatric endocrinologists after diabetes mellitus is for the management of short stature. The majority of those children, mostly boys, have Constitutional growth delay with height age similar to bone age, so an average adult height prognosis is indicated. Our results revealed a statistically significant relationship between growth hormone deficiency among the participants and parents' consanguinity, Hypothyroidism, gender, birth weight, tanner stage, bone age, and NICU admission. Almost fifty-four percent of growth hormone deficiency patients have no parents' consanguinity, while all participants with GHD had no hypothyroidism. Males are more susceptible to GHD than females. Almost all participants with GHD had normal birth weight, while most had low for age tanner stage. Virtually all participants with GHD had delayed bone age, while most had no NICU admission. This goes in line with another study by Essaddam et al[27], who found that GHD was more common in males than in females significantly with a sex ratio of 1.96 (p=0.02). In disagreement with our results, Zayed et al[25] found that the prevalence of GHD in short children with positive consanguinity between their parents was 85.1% compared to 53.2 % in those with negative consanguinity between their parents. They defined consanguinity as a union between parents who are related as second cousins or closer. Our results also align with another study by Kang et al[28] found that bone age is delayed in children with GHD significantly if compared to chronological age. Post-growth hormone treatment results revealed that increasing serum IGF-1 or GH levels stimulates growth plate growth and leads to bone age progression. Our results also align with a study conducted by Sánchez Malo et al. [29], which involved 139 patients with GHD receiving rhGH as treatment. They reported delayed puberty in both genders with GHD. The late menarche and delayed onset of puberty in female patients, which happened later compared to longitudinal studies in healthy children, could be due to the pathophysiology of GHD, because GHD is characterized by proportionate reduced postnatal growth, involving delayed bone age and delayed puberty. Our results revealed a statistically significant association between participants with chronic systemic diseases and PYMS as a reflection of their nutritional status. In agreement with our results, Larson-Nath and Goday[30] found that malnutrition is common in pediatric chronic diseases (chronic kidney disease, cystic fibrosis, congenital heart defects, liver diseases) and impacts outcomes. In children with chronic disease malnutrition is multifactorial and related to the chronic disease itself and non-disease-associated factors.

Conclusion

In conclusion, pathological short stature was more common than non-pathological causes. Growth hormone deficiency was the most common cause of short stature.

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