Ther Adv Endocrinol Metab

2017, Vol. 8(5) 75–80

DOI: 10.1177/2042018817707464

Etiological factors of short stature in children and adolescents: experience at a tertiary care hospital in Egypt

Almontaser Hussein, Hekma Farghaly, Eman Askar, Kotb Metwalley, Khaled Saad, Asmaa Zahran and Hisham A. Othman

Abstract

Background: 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 pediatric endocrinology clinic of Assiut University Children's Hospital, the main tertiary care center in Upper Egypt.

Methods: We conducted this descriptive observational study from May 2012 to December 2015, to analyze 637 children (boys 354, girls 283) with short stature. Evaluation included: detailed medical history, physical examination, laboratory tests, bone age and chromosomal analysis.

Results: Endocrinological causes accounted for 26% of short stature [of them, 11.8% had growth hormone deficiency (GHD)], 63.6% had normal variants of growth [of them, 42% had familial short stature (FSS), 15.8% had constitutional growth delay (CGD) and 5.5% a combination of both]. Interestingly, celiac disease (CD) constituted 6.6% of children with short stature in our cohort.

Conclusions: Although potentially treatable causes such as GHD, hypothyroidism and CD 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. CD is a not uncommon cause of short stature.

Keywords: constitutional growth delay, growth hormone deficiency, short stature

Received: 14 March 2017; revised manuscript accepted: 10 April 2017

Correspondence to:
Khaled Saad
Associate Professor of Pediatrics, Faculty of Medicine, University of Assiut, Assiut 71516, Egypt
khaled.ali@med.au.edu.eg

Almontaser Hussein
Hekma Farghaly
Eman Askar
Kotb Metwalley
Pediatric Department, Faculty of Medicine, Assiut University, Egypt

Asmaa Zahran
Clinical Pathology Department, South Egypt Cancer Institute, Assiut University, Assiut, Egypt

Hisham A. Othman
Department of Clinical Pathology, Faculty of Medicine, Aswan University, Aswan, Egypt

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 pivotal 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 for height.[3] Short stature, although not a disease *per se*, 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 Egyptian 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 Assiut University Children's Hospital, which is the main tertiary hospital in Upper Egypt, and to compare our results with previous studies.

Patients and methods

We conducted this study from May 2012 to December 2015 at the Pediatric Endocrinology Department, and outpatient clinics of the Children's Hospital of Assiut University, a tertiary care center and the largest children's medical center in Upper Egypt with capacity of >500 beds. In this period, 637 children and adolescents from both sexes, 3–16 years of age, having height below two standard deviations (–2SD) or less than 3rd percentile for age and sex were recruited. Patients with contractures and deformities in whom height could not be measured were excluded. Protocol of the study was approved by the ethical committee of Assiut University Children's Hospital. 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 school health sectors all over Upper Egypt to our Pediatric Endocrinology 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 Egyptian growth charts 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/creatinine ratio, antitissue trans-glutaminase (anti-tTG IgA and IgG), stool examination, 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 SD below the mean with or without growth velocity < 4 cm/year or height 2 SD or more below the corrected mid-parental height, and delayed bone maturation), we measured serum insulin-like growth factor-1 (IGF-1) and 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 SD 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,

Table 1. Age and sex distribution of children with short stature.

Age (years)	Total (n = 637)	Males (n = 354)	Female (n = 283)
	n (%)	*n* (%)	*n* (%)
3–6	90 (14.1)	59 (16.7)	31 (11.0)
6–12	406 (63.8)	214 (60.5)	192 (67.8)
12–16	141 (22.1)	81 (22.8)	60 (21.2)

and normal growth hormone (GH) response to provocative testing.[14] Skeletal dysplasia was confirmed 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 immunoradiometric assay (IRMA), while FT3 and FT4 were estimated by radioimmunoassay kits from Diagnosis Product Corporation (Los Angeles, CA, USA).

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/m^2 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.

IGF-1 was determined at diagnosis using solid phase IRMA, using kits from Diagnostic System Laboratories Inc., Texas, USA.

Statistical analysis

Continuous variables were represented as means $\pm$ 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 (α). Confounding variables like age and sex were controlled by stratification.

Results

During the study period, we recruited a total of 637 children and adolescents (354 boys and 238 girls, with a ratio of 1.25:1) with short stature. Their age ranged from 3 to 16 years, with mean age of 9.45 $\pm$ 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 boys was 9.6 $\pm$ 3.9 years with median age of 10 and interquartile age of 8 years, and in girls was 9.3 $\pm$ 3.6 years with median age of 9 and interquartile age of 7 years. The majority (63.8%) of the children were between the age of 6 and 12 years (Table 1). We found familial short stature (FSS) in 42% of the children, constitutional growth delay (CGD) in 15.8%, GHD in 11.8%, hypothyroidism in 9.1%, celiac disease (CD) in 6.6% and idiopathic short stature in 1.7% of the children. We grouped the children according to the etiology of short stature into three major categories: nonpathologic, endocrinological and systemic nonendocrinological (Tables 2–4).

FSS constitutes 68.2 % of nonpathologic causes of short stature in this study. Furthermore, 25.7% of the children had CGD, 3.3% were small for gestational age and in 2.8%, there was idiopathic short stature (Table 2).

The most common endocrinological factor for short stature was GHD (41.6%), followed by

Table 2. Nonpathologic variants of short stature ($n = 393$).

Etiology	*n* (%)
FSS	239 (60.8)
CGD	101 (25.7)
FSS and CGD (coexistent)	29 (7.4)
Idiopathic short stature	11 (2.8)
Small for gestational age	13 (3.3)

CGD, constitutional growth delay; FSS, familial short stature.

Table 3. Endocrinological causes of short stature ($n = 166$).

Etiology	*n* (%)
GHD	75 (45.2)
Primary hypothyroidism	58 (34.9)
Uncontrolled type 1 diabetes	17 (10.2)
Congenital adrenal hyperplasia	3 (1.8)
Pseudohypoparathyrodism	5 (3)
Laron dwarfism	2 (1.2)
Emptysella syndrome	3 (1.8)
Craniopharyngioma	2 (1.2)
Cushing syndrome	2 (1.2)
Precocious puberty	1 (0.6)

GHD, growth hormone deficiency.

Table 4. Systemic nonendocrinological causes of short stature (n =79).

Etiology	*n* (%)
CD	42 (53.1)
Renal tubular acidosis	7 (8.9)
Skeletal dysplasia	5 (6.3)
Turner syndrome	4 (5)
Hypophosphatemic rickets	3 (3.8)
Juvenile rheumatoid arthritis	3 (8.9)
Cystic fibrosis	2 (2.5)
Osteogenesis imperfecta	1 (1.2)
Fanconi anemia	2 (2.5)
Langerhans cell histiocytosis (X)	1 (1.3)
Dysmorphic children with unidentified genetic defects	9 (11.4)

CD, Celiac disease.

hypothyroidism (34.9%) and uncontrolled diabetes (10.2%); Table 3.

Nonendocrinological diseases (Table 4) accounted for 12.4% of cases of short stature; CD was the most common nonendocrinological etiology (21.5%) followed by renal tubular acidosis and juvenile rheumatoid arthritis (8.9% each). Dysmorphic children with short stature accounted for 15.2% of the nonendocrinological causes of short stature; unfortunately, we could not do a comprehensive genetic study to diagnose the specific genetic defect associated with them.

There were 42 children (6.6%), mean age of 9.2 $\pm$ 3.8 years, who had CD (27 boys, 15 girls) with typical findings on intestinal biopsies such as total villous atrophy, an increase in crypt height, and intra-epithelial lymphocyte (IEL) numbers 40 IEL/100 epithelial cells (EC) or more (Type 3C). They presented clinically with failure to thrive and short stature. Gastrointestinal tract symptoms like bouts of diarrhea, unexplained vomiting or abdominal pain were present in all of the children. We performed endoscopy for 50 patients; 8 had nonconclusive intestinal biopsy findings on applying Oberhuber's modified Marsh classification of histologic findings in CD.

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 most common single etiology of short stature found was FSS (37.46%). Furthermore, nonpathologic normal variants of growth constituted 61.6% of short stature children (stratified as 37.5% FSS, 15.8 % CGD, 4.5% having both FSS and CGD, 1.7% idiopathic short stature and 2% small for gestational age) 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, 12.4% 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%.[15,17,18] Furthermore, GHD in our cases constituted 45.2% of the endocrinological causes and 11.8% 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, 12 months.[21]

CD is the most common genetically based disease associated with food intolerance. The classical presentation in children includes gastrointestinal symptoms, usually starting after the introduction of gluten in the diet. CD associated with subnormal growth velocity, delayed bone age, suppressed GH response to provocative tests and short stature might be the only presenting symptom in some children. It should be considered in any child presenting with short stature or failure to thrive, especially with the availability of new, simple, very sensitive and specific serological tests (antigliadin, antiendomysium and antitransglutaminase antibody M assays).[22] In our study, CD accounted for 6.6% (42/637) of the short stature children. Our finding is contradicted by two studies from Saudi Arabia and India reporting a higher prevalence of CD (10.9% and 11%, respectively) in their children.[23,24] Our result, however, is in agreement with a previous study on CD from Egypt with a relatively large number of children in which the authors reported a prevalence of 0.53% in apparently healthy children, 4.7% in children with failure to thrive and 6.4% in adolescent with type 1 diabetes.[25] Growth charts are readily available and are an inexpensive method for following up proper growth in children. We emphasize the importance of accurate and regular height measurement to promptly identify significant decrease in growth velocity in short children with potentially treatable etiology.[26]

Conclusion

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

Acknowledgements

The authors extend their appreciation to all doctors in the rural health facilities who actively referred children and adolescents with suspected growth problems to our hospital. We also extend our deepest thanks to pediatric endocrinology unit and outpatient clinic nursing staff for their continuous support throughout this work.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

References

1. Cakan N and Kamat D. Short stature in children: a practical approach for primary care providers. *Clin Pediatr (Phila)* 2007; 46: 379–385.
2. Kamboj M. Short stature and growth hormone. *Indian J Pediatr* 2005; 72: 149–157.
3. Yadav S and Dabas A. Approach to short stature. *Indian J Pediatr* 2015; 82: 462–470.
4. Rose SR, Vogiatzi MG and Copeland KC. A general pediatric approach to evaluating a short child. *Pediatr Rev* 2005; 26: 410–420.
5. Bhadada SK, Agarwal NK and Singh SK. Etiological profile of short stature. *Indian J Pediatr* 2003; 70: 545–547.
6. Sultan M, Afzal M, Qureshi SM, *et al.* Etiology of short stature in children. *J Coll Physicians Surg Pak* 2008; 18: 493–497.
7. Zargar AH, Laway BA, Masoodi SR, *et al.* An aetiological profile of short stature in the Indian subcontinent. *J Paediatr Child Health* 1998; 34: 571–576.
8. Cohen P, Rogol AD, Deal CL, *et al.* Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. *J Clin Endocrinol Metab* 2008; 93: 4210–4217.
9. Marshall WA and Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 1970; 45: 13–23.
10. Marshall WA and Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969; 44: 291–303.
11. Greulich WW and Pyle SI. *Radiographic atlas of skeletal development of the hand and wrist*. 2nd ed. Stanford, CA: Stanford University Press, 1959.
12. Rhee N, Oh KY, Yang EM, *et al.* Growth hormone responses to provocative tests in children with short stature. *Chonnam Med J* 2015; 51: 33–38.
13. Miller BS and Zimmerman D. Idiopathic short stature in children. *Pediatr Ann* 2004; 33: 177–181.
14. Ambler GR, Fairchild J and Wilkinson DJ. Debate: idiopathic short stature should be treated with growth hormone. *J Paediatr Child Health* 2013; 49: 165–169.
15. Al-Jurayyan NNA, Mohamed SH, Al Otaibi HM, *et al.* Short stature in children: pattern and frequency in a pediatric clinic, Riyadh, Saudi Arabia. *Sudan J Paediatr* 2012; 12: 79–83.
16. Colaco P and Desai M. Identification of a child with short stature. *Indian Pediatr* 1990; 27: 1159–1164.
17. Lashari SK, Korejo HB and Memon YM. To determine frequency of etiological factors in short statured patients presenting at an endocrine clinic of a tertiary care hospital. *Pak J Med Sci* 2014; 30: 858–861.
18. Lindsay R, Feldkamp M, Harris D, *et al.* Utah Growth Study: growth standards and the prevalence of growth hormone deficiency. *J Pediatr* 1994; 125: 29–35.
19. Zayed AA, Mustafa Ali MK, Al-Ani MA, *et al.* The prevalence of isolated growth hormone deficiency among children of short stature in Jordan and its relationship with consanguinity. *Clin Endocrinol (Oxf)* 2014; 81: 876–882.
20. Murray PG, Dattani MT and Clayton PE. Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. *Arch Dis Child* 2016; 101: 96–100.
21. Metwalley KA, Farghaly HS and Abd El-Hafeez HA. Evaluation of left ventricular mass and function, lipid profile, and insulin resistance in Egyptian children with growth hormone deficiency: a single-center prospective case-control study. *Indian J Endocrinol Metab* 2013; 17: 876–882.
22. Bhadada SK, Bhansali A, Ravikumar P, *et al.* Changing scenario in aetiological profile of short stature in India – growing importance of celiac disease: a study from tertiary care centre. *Indian J Pediatr* 2011; 78: 41–44.
23. Assiri AM. Isolated short stature as a presentation of celiac disease in Saudi children. *Pediatr Rep* 2010; 2: e4.
24. Singh P, Sharma PK, Agnihotri A, *et al.* Coeliac disease in patients with short stature: a tertiary care centre experience. *Natl Med J India* 2015; 28: 176–180.
25. Abu-Zekry M, Kryszak D, Diab M, *et al.* Prevalence of celiac disease in Egyptian children disputes the east–west agriculture-dependent spread of the disease. *J Pediatr Gastroenterol Nutr* 2008; 47: 136–140.
26. Tanner JM, Goldstein H and Whitehouse RH. Standard for children's height at ages 2 to 9 years allowing for height of parents. *Arch Dis Child* 1970; 45: 755.