ORIGINAL ARTICLE

SHORT STATURE: WHAT IS THE CAUSE IN OUR POPULATION

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Background: Globally children and adolescents with growth failure are referred to specialized units for evaluation and management. We designed this study to determine the cause of short stature in children and adolescents referred to our endocrine unit for evaluation and further management. **Methods:** This descriptive cross sectional study was performed in the Department of Endocrine, Diabetes and Metabolic Diseases, Hayatabad Medical Complex, Peshawar. Children and adolescents between 2–20 years with height below 2 SDS or less then 3rd percentile for their age and gender were included while those with kyphoscoliosis, thalassemia major, diabetes mellitus type-1 were excluded. Detailed history was obtained followed by detailed physical examination and a pre-set penal of investigations. **Results:** Seventy-three children with mean chronological age of 11.75.3±4.06 years, 56.31% boys and 43.83% girls (p<0.05) were included. Mean height was 117.28±17.55 cm, -4.23±2.06 SDS below for this population age group. Mean parental height was 156.87±11.82 cm, mean bone age was 8.56±4.03 years while mean bone age delay was 3.23±1.94 years. Common causes found were variants of normal growth present in 38.35%. Constitutional Delay of Growth and Puberty (CDGP) were found in 13.7%, Familial Short Stature (FSS) in 11.0% while overlapping features of both in other 13.7%. Isolated Growth Hormone Deficiency (GHD) was found in 23.3%, primary hypothyroidism in 9.6% and pan-hypopituitarism in 2.7%. Common non endocrine causes found were Turner's syndrome, rickets, chronic anaemia, bronchial asthma and achondroplasia. **Conclusion:** Isolated GHD, CDGP and FSS, primary hypothyroidism and Turner's syndrome are the most common causes of short stature in our set up.

Keywords: short stature, Constitutional Delay of Growth and Puberty (CDGP), Familial Short Stature (FSS), Growth Hormone Deficiency (GHD), primary hypothyroidism

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INTRODUCTION

Globally children and adolescents with growth failure are referred to specialized units for evaluation and management; however the criteria for both referral and evaluation for short stature are still controversial.[1]

Short stature is a condition in which height of an individual is below 3rd percentile or more than 2 standard deviations (SDs) below the corresponding mean height for a given age, gender and population group (ethnicity).[2,3] However, other cut-offs are also used in medical practice.[4,5]

In United States 2.2 million children under 18 years of age have heights below the 3rd percentile.[6] Among the children evaluated for short stature pathological cause is identified in only 20%.[2] In Utah Growth Study height and growth velocity of 115,000 American children were assessed and in only 5% children an endocrine cause was found among the 555 with short stature.[7] Other researchers in West also found endocrine cause in only minority of patients.[8,9] Almost 80% of the short stature children are diagnosed with Idiopathic short stature (ISS),[7] a condition characterized by short stature in a child with normal workup, sufficient growth hormone level, normal body proportions, no dysmorphic syndromes, systemic or endocrine disease and good nutritional status.[10–11] ISS in an umbrella term which includes both Familial Short Stature (FSS) where a child is short compared with the reference (general) population but remains within the range of target height (mid parental height) with no bone age delay, normal growth rate (≥25th percentile) and Non Familial Short Stature (FSS), where a child is short compared with the reference population as well as target height, mainly include children with Constitutional Delay of Growth and Puberty (CDGP). CDGP is characterized by short stature, bone age delay (≥2 years), delayed puberty (onset at ≥13 years in girls and ≥14 years in boys), normal growth rate (≥25th percentile) and often family history of delayed puberty. Both FSS and CDGP are considered normal variants of growth often difficult to distinguish, if the child presents early in life, such children finally achieved the target height.[12] Both normal variants of growth FSS and CDGP are considered of ISS in the recent consensus statement definition of ISS.

Worldwide prevalence of GH deficiency (GHD) ranges from 1:4000 to 1:10000, but in few areas higher prevalence has been reported.[13–15] The Utah study reported 33 patients with GHD among the 555 short statured children.[7] GDH can be congenital (autosomal recessive (type IA, IB) autosomal dominant (type IIB), or X-linked (type-III), acquired (secondary to

brain trauma both peri-natal or postnatal, early childhood central nervous system infections, tumours of the hypothalamus or pituitary including pituitary adenoma, craniopharyngioma, glioma, any CNS metastases, radiation therapy to head and neck region, infiltrative diseases like langerhan's cell histiocytosis, sarcoidosis, tuberculosis), or idiopathic (without any identifiable cause).

In addition gene mutation or deletion in the short stature homeobox-containing (SHOX), is described in 1-5% patients labelled as ISS.[16–19] Other described but rarely tested patho-physiological mechanisms involved in short stature individuals include low spontaneous GH secretion in spite of normal GH response in provocation testing, low concentration of GH binding protein (GHBP) resulting in low insulin like growth factor-I (IGF-I) levels and high GH levels (GH insensitivity), GH receptor deficiency, GH inactivating antibodies, defects in GH activation pathways and IGF-1 mutations.

Nutritional deficiencies resulting in short stature are prevalent in 3rd world countries as well in developed communities resulting from self-imposed dietary restriction (anorexia nervosa and other eating disorders). Clinical or biochemical abnormalities are usually not found in subtle nutritional deficiencies neither children are tested for micronutrient deficiencies during evaluation for short stature.[20–23.]

Any chronic disease can cause short stature like renal diseases (CRF, chronic glomerlonephritis), malignancies, pulmonary disease (cystic fibrosis, bronchial asthma), cardiac diseases (congenital heart diseases), gastro-intestinal diseases (coeliac disease, mal absorption syndromes).[24–28] Treatment with glucocorticoids (long term) both systemic and inhaled, chemotherapeutic drugs, radiotherapy, intrauterine conditions like intrauterine growth retardation (IUGR) and foetus small for gestational age (SGA) can also result in short stature.[29–31]

Being the largest and the first endocrine unit in this part of the country, children with growth issues are referred from all over the province for evaluation and diagnosis to our outpatient department. We designed this study to find out in children (population) presenting with short stature (exposure) the frequency of underlying medical disorders (outcome).

MATERIAL AND METHODS

This descriptive cross sectional observation study was conducted in the Department of Endocrine, Diabetes and Metabolic Diseases at Hayatabad Medical complex, Peshawar from September 2014 to August 2015. Children and adolescents of either gender between 2 to 20 years of age who were referred to our outpatient department with height below 2SDs or less then 3rd percentile for their age and gender with reference population were included. Children with contractures, kyphoscoliosis, those who were receiving regular blood transfusions for treatment of beta thalassemia, children with uncontrolled type 1 diabetes mellitus and those who were on renal replacement therapy were excluded. Referred children with height above 3rd percentile were also excluded. Non probability consecutive sampling technique was used and sample size (N=73) was calculated using the WHO software for sample size determination in Health Studies, using one-sample situation, estimating a population proportion with specified absolute precision with the following assumptions. Confidence level (1-α)=95%, anticipated population proportion (P)=0.92, absolute precision (d)=5% (0.05).[32]

Protocol of the study was approved by hospital ethical committee, purpose of the study was explained and informed consent was taken from the parents/guardians and those who weren't willing were also excluded. Detailed history was taken from each participant in presence of both parents preferably (otherwise parent/s were contacted on phone.

Prenatal, birth and childhood history emphasizing on IUGR, twin pregnancy, intrauterine infections, SGA, birth asphyxias, birth trauma, presence of any congenital deformity (including surgically corrected anomalies), breast feeding, delay in developmental milestones and poor school performance was obtained. History of repeated chest infections, chronic diarrhoea, tuberculosis, bronchial asthma, childhood cancer including any CNS tumour, radiation exposure, head trauma, any surgical intervention involving nasopharynx or skull, drug history (chronic use of systemic and inhaled corticosteroid for bronchial asthma, juvenile arthritis, nephrotic syndrome, anti-depressant and anticonvulsants) was recorded. Dietary history was assessed to exclude malnutrition and anorexia nervosa (especially in teenager girls) and other eating disorders.[33] Tempo of puberty in both parents (age at start of pubic hair, growth spurt in father and menarche of mother) was also recorded.

Standing height was measured accurately by keeping child's head in Frankfurt plane while occiput, shoulder, buttocks and heel touching vertical board. Upward pressure was applied on mastoids to measure proper height and plotted accurately on standard Tanner and Davies growth chart.[34] Height was expressed as percentile position with age references and standard deviation score (SDS) and sex-corrected mid parental height (target height) were calculated. Height velocity was not measured as it requires at least two readings 6 months apart. Sitting height, arm span, lower and upper body segments heights were measured to exclude skeletal dysplasia's and SHOX mutation. Weight was recorded while patient was wearing light weighted

clothes. Mid-parental (target) height was calculated using on-line calculator using the following formulae.[35]
For girls (father's height [cm]+mother's height [cm]-13)/2
For boys (father's height [cm]+mother's height [cm]+13)/2

Detailed general physical and systemic examination was performed including examination for secondary sexual characteristics and phenotypic characteristics of any genetic syndromes or skeletal dysplasias. Table-1 All patients underwent a pre-designed panel of investigations including complete blood count with erythrocyte sedimentation rate, red blood cell indices, serum urea and creatinine, liver function tests including serum albumin and alkaline phosphatase, serum electrolytes and calcium, thyroid stimulating hormone (TSH) and free T4 levels, urine routine examination with pH and random blood sugar. IgA anti-tissue transglutaminase antibody (IgA anti TTG antibodies) for coeliac disease was performed in all patients. GH levels after insulin stress test (insulin dose of 0.15- 0.3 units/kg given intravenously and baseline, post hypoglycaemia levels at time 0, 30, 60 and 90 mins) were performed. Karyotying in female patients was done, if the preceding investigations were normal or there was strong clinical suspicion of Turner's syndrome. Serum FSH, LH, and estradiol levels were performed in girls of more than 12 and testosterone levels in boys more than 13 years for delayed puberty or if there was suspicion of pan-hypopituitarism. Vitamin D level was ordered in those with low calcium and/or raised alkaline phosphatase levels. Skeletal maturity (bone age) was estimated from X-ray of non-dominant hand and wrist, using Greulich and Pyle radiological atlas for development of hand and wrist by an experience radiologist.[36,37] All the above mentioned information including name, age and gender were recorded in the study *pro forma.* Strict exclusion criteria were followed to control confounders and bias in study results. Data collected were entered in SPSS 16. Mean±SD was calculated for continuous variable like age, height categorical variable like gender, diagnosis were expressed as frequencies and percentages. Cross tabulation of gender was done with most common outcome variables.

RESULTS

A total of 73 children with mean chronological age of 11.75.3±4.06 years, 41 (56.31%) boys and 32 (43.83%) girls were enrolled (p<0.05). Mean height was 117.28±17.55 cm, which was 4.23±2.06 SDS below for this population age group. Mean parental height was 156.87±11.82 cm, mean bone age of 8.56±4.03 years while mean bone age delay of 3.23±1.94 years. (Table-2).

Boys were presented at earlier age 10.57±3.72 compared to girls, 13.36±4.03 years. (p-0.004). Mean bone age in boys (7.38±3.81) was significantly lower compared to girls (9.84±3.94) (p-0.009).

Frequency of normal variants of growth, endocrine, non-endocrine causes are shown in table-3. Most common causes found were variants of normal growth patterns, found in 28 (38.35%) children. CDGP in 10 (13.7%), FSS in 8 (11.0%) and overlapping features of both CDGP and FSS in 10 (13.7%). Among the endocrine causes the most common causes were isolated GHD found in 17 (23.3%) children followed by primary hypothyroidism in 5 (9.6%) and pan-hypopituitarism 2 (2.7%) children. Common non endocrine causes of short stature were Turner's syndrome found in 5 (6.84%), rickets/vitamin D in 4 (5.47%), chronic anaemia in 3 (4.10%) children. Among others bronchial asthma, achondroplasia and malnutrition found each in 2.7% and IUGR in one child. Cross tabulation of the common causes of short stature with gender is given in table-4.

Table-1: Clinical features of genetic syndromes/Skeletal dysplasias

Dysmorphic feature	Associated syndrome/ skeletal dysplasias
Webbed neck, cubiti valgi, heart murmur (biscupid aortic valve, co-arctation of aorta), multiple navi, inverted, hypoplastic and wide spaced nipples, lymphadema (congenital), nail convexity/dysplasia, ptosis, scoliosis.	Turner Syndrome
Triangular shaped face, hypertelorism, strabismus, down-slanting palpebral fissures, low-set ears, webbed neck, heart murmur (pulmonary stenosis), cryptorchidism, ptosis, high nasal bridge, hepatosplenomegaly.	Noonan Syndrome
Small hands/feet, muscular hypotonia, micro penis, cryptorchidism, feeding difficulties, poor growth, and delayed development. hyperphagia, obesity, narrow forehead, light-coloured, hair, underdeveloped genitalia, delayed puberty.	Prader-Willi Syndrome
Asymmetry of face/arm/legs, small triangular face, clindodactyly, hemi-hypertrophy, asymmetry of the limbs, blue sclerae, high forehead that tapers to a small jaw, micrognathia, prominent nasal bridge, down-turning corners of the mouth.	Russell Silver Syndrome
Cleft lip/palate, micro penis, single central incisor,	Congenital GHD
Flat occiput, flattened facial appearance, brachycephaly, epicanthal folds, flat nasal bridge, upward-slanting palpebral fissures, protruding tongue, small dysplastic ears, diastasis recti, single transverse palmar crease, short fifth finger with clinodactyly, wide space between the first and second toes, shortened extremities, joint hyperextensibility, neuromuscular hypotonia, dry skin, congenital heart defects.	Down Syndrome
Short stature, mesomelia (middle portion of a limb is shorted in relation to the proximal portion) and Madelung deformity (abnormal alignment of the radius, ulna, and carpal bones at the wrist)	SHOX mutation Leri-Weill dyschondrosteosis (LWD).
Enlarged neurocranium, frontal bossing, flattening of the nasal bridge, mid face hypoplasia, prominent mandible, flattened anteroposterior diameter of the chest, protruding abdomen.	Achondroplsia/ Hypochondroplsia

Table-2: Demographic Features of Study Population (N=73)

Demographic Features	Females	Male	Total	*p*-valve
Mean Age (years)	13.36±4.03	10.57±3.72	11.75.3±4.06	0.004
Height (cm)	119.97±15.28	115.17±19.05	117.28±17.55	0.249
SDS	-4.48±2.32	-4.03±1.84	-4.23±2.06	0.365
Percentile	0.34±0.57	0.54±0.76	0.46±0.68	0.215
Bone Age	9.84±3.94	7.38±3.81	8.56±4.03	0.009
Bone Age Delay	3.35±1.73	3.13±2.10	3.23±1.94	0.627
Age groups				
1–5	00	02	02 (2.7%)	
6–10	08	16	24 (32.9%)	0.007
11–15	10	19	29 (39.7%)	
>15	14	4	18 (24.7%)	

Table-3: Frequency of Different causes

Diagnosis	Total
Normal Variants of growth	28 (38.35%)
Constitutional Delay of Growth and Puberty	10 (13.7%)
Familial Short Stature (FSS)	08 (11.0%)
Features of both CDGP/FSS	10 (13.7%)
Endocrine Causes	26 (35.61%)
Growth Hormone Deficiency (GHD)	17 (23.3%)
Primary hypothyroidism.	7 (9.6%)
Pan-hypopituitarism.	2 (2.7%)
Non Endocrine Causes	19 (26.02%)
Turner Syndrome	5 (6.84%)
Rickets	4 (5.47%)
Anaemia	3 (4.10%)
Achondroplasia	2 (2.7%)
Asthma	2 (2.7%)
Malnutrition	2 (2.7%)
IUGR	1 (1.3%)

Table-4: Cross Tabulation of Different Causes with Gender

Diagnosis	Male	Female	Total	*p*-valve
Growth Hormone Deficiency (GHD)	14	3	16	**0.01**
Constitutional Delay of Growth and Puberty (CDGP)	7	3	10	0.26
Familial Short Stature (FSS)	7	1	8	0.06
Features of both CDGP/FSS	6	4	10	0.56

DISCUSSION

The prevalence and outcomes of short stature children are well studied and established in Western world.[38-40] 3% of normal population will fall below 2SDs in any reference population as per definition, so neither all children with short stature require extensive evaluation nor pathological cause is found in all those who are investigated. In study conducted by Lashari SK *et al*[41], mean age of participants was 9.9±3.4 years compared to our study where mean age was 11.75.3±4.06. Age range was from 5–20 years which differs slightly from others.[42] Forty-one (56.16%) were males and 32 (48.83%) were females ($p<0.005$). In our studied population male to female ratio was 1.34:1, compared to 1.08:1 by Lashari SK *et al*[41] and 1.17:1 by Rabbani MW *et al*[42]. Most of the children (72.60%) were between 6–15 years of age, mostly because of parents' late recognition of growth failure. Rabbani MW *et al*[42] reported 76.3% patients presented to them within the same age group. Basic reason for late presentation in Pakistani population is lack of maintaining proper developmental record compared to Western populations where presentation is at much younger age. Accurate growth records (plotted growth chart) were provided by only 1 participants and only 19.2% parents could recall details of antenatal, neo-natal and early childhood history compared to Western reports where almost 50% participant provided complete growth record.[43] If provided, complete and detailed growth record may help distinguish patients in whom evaluation is required from those who can be observed overtime.[44–46]

Mean height was -4.23±2.06 years SDS below for the age-gender matched population and mean percentile was well below age-gender matched population (0.46±0.68 percentile). Compared to others these children have lower SDS and are at lowest extreme of height with significant growth delay. Social circumstances, poverty, lack of education and health awareness may be possible reasons where marginally taller yet short stature children are not shown to clinicians or referred to specialized centres

Normal variants of growth were the most common reason for growth failure as a group, 28 (38.35%) referred children had either FSS 08 (11.0%), CDPG (10 (13.7%) or overlapping features of both, 10 (13.7%). Unfortunately, growth velocity was not measured as it requires, minimum of 6 months follow up and we evaluated the referred children at single contact. In CMH Multan normal variants of growth were diagnosed in 37.4%[42] and Sultan M *et al*[47] reported same prevalence. FSS was diagnosed in 11.0% compared to 21.3% by Rabbani MW *et al*[42] and 15% by Sultan M *et al*[47]. CDGP was diagnosed in 13.7% compared to 17.3% by Sultan M *et al*.[47] Lindsey *et al*[6] reported normal variants in 80%, Moayeri H *et al*[38] in 47% a much higher prevalence than sub continental studies.

Among the endocrine causes isolated GHD (peak GH levels of <10 ng/dl on insulin stress test) was the most common cause present 17 (23.3%) of the children and adolescents, whereas other researchers, Rabbani MW *et al*[42], Moayeri H *et al*[38] Zarger *et al*[24] and Awan TM *et al*[48] diagnosed GHD as cause of short stature in 10.7% 23.4%, 22.8% and 13.9% children

respectively. GHD was more common in boys compared to girls (p<0.05) Primary hypothyroidism as cause of growth failure was found in 7 (9.6%) patients among them 3 were diagnosed but inadequately treated children while rest 4 were diagnosed as hypothyroid during present workup. 17.2% children were hypothyroid with Rabbani MW *et al*[42], 7.8% in Zargar AH *et al*[24]. Panhypopiuitarism was diagnosed in 2 (2.7%) unfortunately both were operated for crainopharyngeoma in early childhood. Bhadada SK *et al*[25], reported panhypotuiutarism in 1.1% (n=352). Collectively 26 (35.61%) patient had an endocrine cause in our study compared to 22.7% reported by Bhadada SK *et al*[25], 27.9% by Rabbani MW *et al*[42]. In Utah study only 5% patient had a recognize endocrine cause which is quite a contrast to observation by many others including ours, possible explanation for this disparity is that Utah was conducted on general population, while we selected referred patient to specialized unit and our mean SDS was much lower than Utah study group.[7]

Non endocrine causes were present in remaining 26 (35.61%) compared to 18.2% by Zargar AH *et al*[24] and 32.8% by Bhadada SK *et al*[25]. Turner's syndrome was diagnosed in 5 (6.84%). Three patients had stigmata of this congenital syndrome while the other 2 girls had no clinical feature of turner syndrome. Bhadada SK *et al*[26], Colaco P *et al*[39] and Lashari SK *et al*[41] reported in prevalence of turner syndrome in 7.5%, 7.4%, and 3% respectively. 2.7% had characteristic features of achondroplasia (classical clinical and x-ray findings, genetic testing wasn't available) and 4 (5.47%) children had vitamin-D level <10 ng/dl among 4 checked for (low calcium and raised alkaline phosphatase) vitamin-D deficiency. Others has reported the presence of skeletal dysplasias including rickets in 6.5% and 5.7%.[38,39] Finally, chronic illnesses was found culprit in 9.9% (bronchial asthma, chronic anaemia, malnutrition) of the cases compared to 21.3% reported by Rabbani MW *et al.*[42] Surprisingly, coeliac disease and congenital heart diseases were not found in any patient.

CONCULSION

In conclusion, isolated GHD, primary hypothyroidism and panhypopituitarism are the three most common endocrine causes of short stature but still they are not as common as normal variants of growth (FSS and CDPG) as a group. Most of children who present with growth failure in our setup are at much lower SDS compared to Western population and the likely hood of finding a pathological cause is more comparatively. Finally, maintaining proper birth and childhood records can help treating physicians to refer selected children and adolescents for further evaluation to specialist clinics.

Parents couldn't recall birth weight and length of their kids nor were the birth records of majority of the children were available. None but only parents of only one kid could produce growth charts of their children. Unfortunately, available growth records were incomplete in majority of the children so IUGR and SGA children were not excluded effectively, however, similar short comings were encountered by Grimberg *et al*[44] as well, while others have reported prevalence of SGA and IUGR.[25,26,40] SHOX gene mutation or deletion analysis is unavailable in our setup that might have been present in some as the prevalence has been reported to be 1–5% in children diagnosed as ISS (CDGP and FSS).[17–20] Growth velocity wasn't measured in our study. Vitamin D levels weren't ordered in all patients keeping in view of high cost and very high prevalence of vitamin D deficiency in general paediatrics population.

AUTHOR'S CONTRIBUTION

FM: Abstract writing, concept of study, study design, data collection, writing results, discussion, data analysis. AKA: Writing introduction, discussion, reference writing, and data analysis. IA: Data collection, IST performance. TG: Writing conclusions, discussion and data collection. AHA: Formatting study design, final review.

REFERENCES

1. Deodati A, Cianfarani S. Impact of growth hormone therapy on adult height of children with idiopathic short stature: systemic review. BMJ 2011;342:c7157.
2. Schnell FN, Bannard JR. Short Stature in Childhood and Adolescence: Part 1: Medical management. Can Fam Physician 1991;37:2206–13.
3. Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, *et at*. Consensus statement on diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormones Research Society, and Lawson Wilkins Pediatric Society, and the European Society for Paediatric Endocrinology workshop. J Clin Endocrinol Metab 2008;93(11):4210–17.
4. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, *et al*. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics 2002;109(1):45–60.
5. Freeman JV, Cole TJ, Chinn S, Jones PRM, White EM, Preece MA. Cross sectional stature and weight reference curves for the UK.1990. Arch Dis Child 1995;73(1):17–24.
6. Bender MK. Centers for Disease Control and Prevention growth charts versus breastfeeding? Pediatrics 2002;110(3):648–8.
7. Lindsay R, Feldkamp M, Harris D, Robertson J, Rallison M. Utah Growth Study: growth standards and the prevalence of growth hormone deficiency. J Pediatr 1994;125(1):29–35.
8. Ahmed ML, Allen AD, Sharma A, Macfarlane JA, Dunger DB. Evaluation of a district growth screening programme: the Oxford Growth Study. Arch Dis Child 1993;69(3):361–5.
9. Voss LD, Mulligan J, Betts PR, Wilkon TJ. Poor growth in school entrants as an index of organic disease: the Wessex growth study. BMJ 1992;305(6866):1400–2.
10. Ranke MB. Towards a consensus on the definition of idiopathic short stature. Horm Res 1996(suppl 2):64–6.
11. Wit JM, Ranke MB, Kelner CJH. ESPE Classification of paediatric endocrine diagnoses. Horm Res 2007;68(Suppl 2):1–120.
12. Wit JM, Clayton PE, Rogol AD, Savage MO, Saenger PH, Cohen P. Idiopathic Short Stature: definition epidemiology

and diagnostic evaluation. Growth Hormone IGF Res 2008;18(2):89–110.
13. Jancevska A, Gucev ZS, Tasic V, Pop-Jordanova N. Growth hormone deficiency (GHD) and small for gestational age (SGA): genetic alterations. Prilozi 2009;30(2):33–55.
14. De Mel T. A Study of short stature in a community of Sri Lankan children. 1987:136.
15. de Mel T, Warnasooriya N, Fonseka C. Growth hormone deficiency in Sri Lanka: a preliminary study. Ceylon Med J 1991;36(3):95–7.
16. Binder G. Short stature due to SHOX deficiency: genotype, phenotype and therapy. Horm Res Paediatr 2011;75(2):81–9.
17. Rosillo M, Huber-Lequesne C, Sapin H, Carel JC, Blum WF, Cormier-Diare V. Genotypes and phenotypes of children with SHOX deficiency in France. L Clin Endocrinol Metab 2012;97(7):1257–65.
18. Benito-Sanz S, Aza-Carmona M, Rodrigueaz-Estevez A, Rica-Etxebarria I, Gracia R, Campos-Barros A, *et al*. Identification of the first PAR1deletion encompassing upstream SHOX enhancers in a family with idiopathic short stature. Eur J Hum Genet. 2012;20(1):125–127.
19. Hardin DS. Treatment of short stature and growth hormone deficiency in children with somatotropin (rDNA origin). Biologics 2008;2(4):655–61.
20. Lifshitz F, Botero D. Worrisome growth. In: Lifshitz F, editor. Pediatric Endocrinology. 5th edition. Vol. 2. New York, NY, USA: Marcel Dekker; 2007. p.1–46.
21. Kuszmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, *et al*. CDC growth charts: United States. Adv Data 2000;8(314):1–27.
22. Abdenur JE, Pugliese MT, Cervantes C, Fort P, Lifshitz F. Alterations in spontaneous growth hormone (GH) secretion and the response to GH-releasing hormone in children with nonorganic nutritional dwarfing. J Clin Endocrinol Metab 1992;75(3):930–34.
23. Zimmermann MB, Jooste PL, Mabapa NS, Mbhenyane X, Schoeman S, Biebinger R, *et al*. Treatment of iodine deficiency in school-age children increases insulin-like growth factor (IGF)-I and IGF binding protein-3 concentrations and improves somatic growth. J Clin Endocrinol Metab 2007;92(2):437–42.
24. Zargar AH, Laway BA, Masoodi SR, Wani AI, Salahuddin M. An etiological profile of short stature in the Indian subcontinent. J Paediatr Child Health 1998;34(6):571–6.
25. Bhadada SK, Agrawal NK, Singh SK, Agrawal JK. Etiological profile of short stature. Indian J Paediatr 2003;70(7):545–7.
26. Halac I, Zimmerman D. Evaluating short stature in children. Pediatr Ann 2004;33(3):170–6.
27. Waheed KA, Irfan K, Ahmad TM, Khan HI. Spectrum of clinical presentation of chronic renal failure in children. Pak Paediatr J 2002;26:167–71.
28. Queiroz MS, Nery M, Cançado EL, Gianella-Neto D, Liberman B. Prevalence of celiac disease in Brazilian children of short stature. Braz J Med Biol Res 2004;37(1):55–60.
29. Checkley W, Epstein LD, Gilman RH, Cabrera L, Black RE. Effects of acute diarrhea on linear growth in Peruvian children. Am J Epidemiol 2003;157(2):166–75.
30. Lam WF, Hau WL, Lam TS. Evaluation of referrals for genetic investigation of short stature in Hong Kong. Chin Med J (Engl) 2002;115(4):607–11.
31. Rogol AD. Causes of short stature. In: Rose BD, (edi). Up-to date 15.1 [CD Rom]. Waltham MA: upto-date; 2007.
32. Giovenale D, Meazza C, Cardinale GM, Sposito M, Mastrangelo C, Messini B, *et al*. The prevalence of growth hormone deficiency and celiac disease in short children. Clin Med Res 2006;4(3):180–3.
33. Rose SR, Vogiatzi MG, Copland KC. A general pediatric approachto evaluating a short child. Pediatr Rev 2005;26(11):410–20.
34. Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for North American children. J Pediatr 1985;107(3):317–29.
35. Tanner JM, Goldstein H, Whitehouse RH. Standards for children's height at ages 2-9 years allowing for heights of parents. Arch Dis Child 1970;45(244):755–62.
36. Grote FK, Oostdijk W, de Muinck Keizer-Schrama SM, Dekker FW, Verkerk PH, Wit JM. Growth monitoring and diagnostic work-up of short stature: an international in ventorization. J Pediatr Endocrinol Metab 2005;18(11):1031–8.
37. Greulich WW, Pyle SI. Radiographic Atlas of Skeletal Development of Hand and Wrist, 2nd ed. Stanford. Stanford University Press; 1959.
38. Moayeri H, Aghighi Y. A prospective study of etiology of short stature in 426 short children and adolescents. Age 2004;14(1.7):13–3.
39. Colaco P, Desai M. Identification of a child with short stature. Indian Paediatr 1990;27(11):1159–64.
40. Voss LD, Bailey BJ, Mulligan J, Wilkin TJ, Betts PR. Short stature and school performance -- the Wessex growth study. Acta Paediatr Scand Suppl 1991;377:29–31.
41. Lashari SK, Korejo HB, 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(4):858–61.
42. Waqar Rabbani M, Imran Khan W, Bilal Afzal A, Rabbani W. Causes of short stature identified in children presenting at a tertiary care hospital in Multan Pakistan. Pak J Med Sci 2013;29(1):53–7.
43. Grimberg A, Kutikov JK, Cucchiara AJ, Sex difference in patients referred for evaluation of poor growth, J Pediatr 2005;146(2):212–6.
44. Himes JH. Minimum time intervals for serial measurement of growth in recumbent length or stature of individual children. Acta Paediatr 1999;88(2):120–5.
45. Consideration related to the use of recombinant growth hormone in children. American Academy of Paediatrics committee on drugs and committee on bioethics. Pediatrics 1977;99(1):122–9.
46. Hardin DS, Woo J, Butsch R, Huett B. Current prescribing practice and opinions about growth hormone therapy: results of nationwide survey of paediatrics endocrinologist. Clin Endocrinol 2007;66(1):85–94.
47. Sultan M, Afzal M, Qureshi SM, Aziz S, Lutfullah M, Khan SA, *et al*. Etiology of Short Stature in Children. J Coll Physicians Surg Pak 2008;18(8):493–97.
48. Awan TM, Sattar A, Khattak EG. Frequency of growth hormone deficiency in short statured children. J Coll Physicians Surg Pak 2005;15(5):295–8.

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