ORIGINAL ARTICLE

FREQUENCY OF IDIOPATHIC SHORT STATURE AT PEDIATRIC ENDOCRINE CLINIC IN A TERTIARY CARE HOSPITAL AT LAHORE

MUHAMMAD USMAN[1], SOMMAYYA AFTAB[2], ABID RAFIQ CHAUDHRY[3], AAMER NASEER[4], RAFIA GUL[5], TAEED AHMED BUTT[6]

[1,5]Assistant Professor of Pediatrics, FMH College of Medicine & Dentistry, Lahore. [2]Assistant Professor of Endocrinology, FMH College of Medicine & Dentistry, Lahore., [3,4]Associate Professor of Pediatrics, FMH College of Medicine & Dentistry, Lahore, [6]Professor of Pediatrics, FMH College of Medicine & Dentistry, Lahore

ABSTRACT

Background: Short stature is "Height less than 2 standard deviations (2SD) or less than 3rd percentile of the mean height for age and gender. Idiopathic short stature (ISS) must exclude all the explained causes of growth failure including nutritional, systemic illnesses, endocrine, syndromic, skeletal dysplasia, Psychosocial, constitutional and familial. The idea of this study is to know the burden of ISS in our population.

Objective: To determine the frequency of idiopathic short stature in children coming to pediatric endocrine outdoor in a tertiary care hospital for evaluation of short stature.

Methods: This retrospective cross-sectional study was conducted on 188 patients between 2-18 years including both genders, with height below 3rd percentile of age and sex. Their physical, biochemical, hormonal parameters, radiological bone age and Karyotype where indicated was recorded in pre-designed pro-forma. The data was analyzed in SPSS version 25. The frequency and percentages were calculated for qualitative variables such as gender and the cause of short stature.

Results: Among 188 patients of short stature, 100 (53.2%) were males and 88 (46.8%) were females. Idiopathic short stature was found in 10 (5.3%) patients. Among these 10 patients of ISS, 2(20%) were males and 8(80%) were female. Moreover, in cases of ISS, 5(50%) were pre-pubertal, 3(30%) were peri-pubertal and 2(20%) were post pubertal.

Conclusion: ISS is a diagnosis of exclusion. It is more common in females and in the pre-pubertal age group. ISS needs extensive studies to identify its genetic factors and response to human growth hormone (hGH).

Key words: Idiopathic Short stature (ISS), Constitutional delay of growth and puberty (CDGP), Familial short stature (FSS), Growth hormone deficiency (GHD), Human growth hormone (hGH)

How to cite this article: Usman M, Aftab S, Chaudhry AR, Naseer A, Gul R, Butt TA. Frequency of Idiopathic Short Stature at Pediatric Endocrine Clinic in A Tertiary Care Hospital at Lahore. Pak Postgrad Med J 2024;35(3): 96-100

DOI: https://doi.org/10.51642/ppmj.v35i03.581

Correspondence to: *Muhammad Usman*
Assistant Professor of Pediatrics, FMH College of Medicine & Dentistry, Lahore, Pakistan

Email: *umah6174@gmail.com*

INTRODUCTION

Short stature in children is a very common concern of the parents in developing countries.[1] Thez prevalence of short stature is 2.5-3% of children in the world.[2] While in Pakistan the prevalence of short stature is 16.5% in age group of 6-12 years.[3] Children and adolescents with growth failure are referred to pediatric endocrine clinics for the evaluation and treatment. Short stature is "the height which is below 2 standard deviations (S.D.) or below 3rd percentile of the mean height of age and gender".[4] Short stature is not a disease but a sign of many underlying diseases.[5]

Common causes of short stature mentioned in literature are constitutional, familial, growth hormone deficiency, hypothyroidism and celiac disease.[6] 60%-80% of the children coming to pediatric endocrinology outpatient department for assessment of short stature are still labeled as idiopathic.[7] But this group includes the

major proportion that is constitutional delay of growth and puberty and familial short stature according to many other local and international studies as well.

In real sense, idiopathic short stature must exclude all the explained causes of growth failure including nutritional, systemic illnesses, endocrine, syndromic, skeletal dysplasia, Psychosocial, constitutional and familial. The familial short stature (FSS), constitutional delay of growth and puberty (CDGP) and Intrauterine growth retardation (IUGR) with usual later catch-up growth, are actually normal variants of short stature (NVSS).[8] We do come across such idiopathic cases of unexplained growth failure in our practice where the children are healthy, parents do not have short stature and the children fall >2SD of their mid-parental height without any justification. So, they don't even fall into the category of Familial or constitutional short stature.

In different international studies many genetic factors of idiopathic short stature have been identified up till now. The isolated haplo-insufficiency of the SHOX gene is the most common cause of short stature which is identified by monogenic mutations. Its heterozygosity has been documented in 2-15% of idiopathic short stature.[9] However, many cases of ISS are still idiopathic and need genetic identification to tailor the treatment. hGH therapy has been recommended in some countries for treatment of ISS. To have the better results of human growth hormone (GH) for the treatment of ISS, combined trials of hGH with aromatase inhibitors, GnRH analogues or IGF-I have been conducted.[10]

The rationale of this study is to know the burden of idiopathic short stature in the children and adolescents referred to our endocrine OPD for the assessment. Over a period of time, we expect to discover many genes for the identification of idiopathic causes of short stature in these patients. These discoveries will definitely have a big impact on the evaluation and treatment of ISS, to have a better outcome.

OBJECTIVE

To determine the frequency of idiopathic short stature in children coming to pediatric endocrine outdoor in a tertiary care hospital for evaluation of short stature.

METHODS

This retrospective cross-sectional study was conducted in the Pediatric endocrine outpatient department of Fatima Memorial Hospital, Shadman, Lahore. Hospital record from January 2019 to December 2020 was reviewed. Total 188 children were selected by non-probability consecutive sampling technique using 5% level of significance, 2% margin of error and 2% prevalence of short statured children.[7]All the patients of age 2-18 years among both the sex with short stature, that is height below 3rd percentile of age and sex, were included. All the patients already diagnosed as any chronic ailment like cardiac, renal, pulmonary, gastrointestinal, neurologic or endocrine disorders before enrolment and patients who have gross skeletal deformities, disproportionate stature and disorder of sexual differentiation were excluded. Approval of Institutional Review Board and ethical committee was taken before the collection of data.

The data was recorded on predesigned proforma. The data included birth weight, current weight, current height, parental heights, mid-parental height, tanner staging for SMR and age of menarche in adolescent girls. Investigations included X-Ray left wrist and hand for Bone age (by using "Greulich and Pyle atlas"), CBC, Serum electrolytes, bone biochemistry, SGPT, Creatinine, urine C/E and in selected cases where bone age was delayed, Anti-tissue transglutaminase (Anti-tTG IgA & IgG), thyroid profile and serum IGF1 levels. Karyotype was done in girls to rule out turner syndrome. Stimulated growth hormone levels after insulin tolerance test in selected cases with significantly delayed bone age was also documented.

Height was measured with the Harpenden stadiometer in centimeter. Weight was measured with the electronic weighing scale in decimals of Kilogram. We calculated the predicted target height (Mid-parental height) by using the Tanner-Whitehouse method, that is, Target mid-parental height = [father's height (cm) + (mother's height (cm) + 13)] divided by 2 for boys and [(father's height (cm) – 13) + mother's height (cm)] divided by 2 for girls.[11]

SPSS version 25 was used for the data entry and analysis. Frequency and percentages were calculated for qualitative variables such as gender and the causes of short stature including Constitutional delay of growth and puberty (CDGP), familial short stature (FSS), growth hormone deficiency (GHD), Celiac Disease (CD), Hypothyroidism and idiopathic short stature. Quantitative variables of the study such as age and number of cases for individual diagnosis were expressed as mean and standard deviation.

Growth hormone deficiency (GHD) was considered in cases where child was significantly short with low PHV, bone age delay of more than 2year with respect to the chronological age, low IGF1 levels and stimulated (Insulin tolerance test) GH levels < 5ng/dl. **Hypothyroidism** was considered in cases where Low fT4 and High TSH was seen. **Celiac disease** was considered in short children with raised Anti-tTG and positive jejunal biopsy. Short patients who have poor nutritional history and weight for age below 60% of normal, according to NCHS (National Child Health Services) standard, in the absence of any chronic disease, were labeled as **Primary 3rd degree Malnutrition**.

Constitutional short stature was considered in cases where child was short with delayed bone age but height age corresponds to the bone age and peak height velocity was normal. **Familial short stature** was considered in cases where child was short but falls within 2SD of mid-parental height and bone age corresponds to the chronological age.

And the patients in our data who had height less than 3rd percentile of mean and moreover his/her height is less than 2 standard deviations (S.D.) of mid-parental height and bone age corresponds to the chronological age in the absence of any cause were considered **idiopathic short stature**.[12]

RESULTS

Among the total 188 children who have height less than 3rd centile on 2000 CDC growth charts, 100 (53.2%) were males and 88 (46.8%) were female, making 1.13:1 male to female ratio. In our study population, height of the cases varied from 76.5cm to 161cm between 2 to 18 years, father height varied between 143cm to 184cm, maternal height varied between 134cm to 173cm, and mid-parental height varied between 143cm to 181cm. Here, mean father height was 167.4 ± 6.2cm,

mean mother height was 153.2 ± 6.3 cm and the mean mid-parental height was 161± 8 cm.

Table 1. Causes and gender distribution of short stature

	Gender		Total among the cause	%age among all the cause
	Male	Female		
Idiopathic Short Stature	2 20%	8 80%	10 100%	10 5.3%
Familial short stature	27 40.9%	39 59.1%	66 100%	66 35.1%
Constitutional Short Stature	51 66.2%	26 33.8%	77 100%	77 41%
Growth Hormone Deficiency	12 70.6%	5 29.4%	17 100%	17 9%
Celiac Disease	6 75%	2 25%	8 100%	8 4.3%
Hypothyroidism	2 28.6%	5 71.4%	7 100%	7 3.7%
Turner syndrome	0 0%	1 100%	1 100%	1 0.5%
3rd Degree PCM	0 0%	2 100%	2 100%	2 1%
Total	100 53.2%	88 46.8%	188 100%	188 100%

Idiopathic short stature was found in 10 (5.3%) patients. Among these 10 patients with idiopathic short stature, 8(80%) were female and 2(20%) were male. Causes of short stature in rest of the cases in decreasing frequency included, 77(41%) constitutional short stature, 66 (35.1%) Familial short stature, 17(9%) Growth hormone deficiency, 08 (4.3%) celiac disease, 07(3.7%) Hypothyroidism, 02(1.1%) Primary 3rd degree malnutrition and 01(0.5%) Turner syndrome. All the causes and their gender distribution has been shown in table 1.

Among the cases of idiopathic short stature, normal birth weight (2.5-4Kg) was found in 5 (50%) cases and low birth weight (<2.5Kg) in 3 (30%) while in 2(20%) cases parents did not know about the birth weight.

Among all the patients of short stature, 70 (37.2 %) children were having age between 2-8years (pre-pubertal), 94 (50%) children were 8-14years (peri-pubertal), while the remaining 24(12.8%) children were >14 years (post-pubertal). Among the cases of idiopathic short stature, 5(50%) cases were pre-pubertal, 3(30%) cases were peri-pubertal and 2(20%) cases were post pubertal (Table number 2).

Table 2: Causes of short stature with age distribution:

	Age category		
	< 8 years	**8-14 years**	**>14 years**
Idiopathic Short Stature	5 50%	3 30%	2 20%
Familial short stature	22 33.3%	36 54.5%	8 12.1%
Constitutional Short Stature	28 36.4%	37 48.1%	12 15.6%
Growth Hormone Deficiency	4 23.5%	12 70.6%	1 5.9%
Celiac Disease	5 62.5%	2 25.0%	1 12.5%
Hypothyroidism	4 57.1%	3 42.9%	0 0%
Turner syndrome	0 0%	1 100%	0 0%
3rd Degree PCM	2 100%	0 0%	0 0%
Total	70 37.2%	94 50%	24 12.8%

DISCUSSION

Human Growth depends on many factors like Nutrition, hormones, genetics and the environment. Height and weight are the two important objective parameters of the growth and health. For the assessment of growth of these two parameters at an interval, accurate measurement with properly calibrated measuring equipment by a single observer is mandatory. Failing of which may lead to unnecessary investigations and undue stress on the individual and the parents as well.

Short stature is not a disease but it can be a clinical sign of so many underlying diseases. The etiology of short stature include normal variants like familial short stature (FSS) and constitutional delay of growth and puberty (CDGP) where child final height potential is within 2SD of Mid-parental height (MPH) and pathological

conditions like endocrine and chronic systemic ailments where the patient can have a compromised final height below the 2SD of MPH. So, it is important to assess the cause early, to medically intervene and catch up the target height possibly at 50th centile of MPH before the epiphyseal fusion. There are some short statured cases who have no identified cause of their short stature and their height also may be compromised to less than 2SD of MPH. These patients have actually idiopathic short stature.

In this study, among the 188 cases of short stature 100 (53.2%) were boys and 88 (46.8%) were girls with 1.13:1 male to female ratio. In another study on etiologies of short stature done by Al-Jurayyan etal, the ratio between male and female was 1.3:1.[13] Short stature was found to be more common in peri-pubertal age group 94 (50%) as compared to pre-pubertal 70 (37.2%) and post-pubertal 24 (12.8%) age groups.

Out of all the 188 cases, 10 (5.3%) were found to have idiopathic short stature (ISS). Idiopathic short stature was found to be more common in girls, 8 (80%) cases, as compared to boys, 2 (20 %) cases. Moreover, ISS was found to be more common in pre-pubertal age group, 5(50%) cases, as compared to peri-pubertal, 3 (30%) cases and post-pubertal 20 (20%) cases.

When we look at the other causes of short stature in our study population, 143 (76.1%) cases were having normal variants of short stature (NVSS) that is CDGP and FSS, while 17 (9%) were Growth hormone deficiency (GHD), 8 (4.3%) celiac disease, 7 (3.7%) hypothyroid, 2 (1%) primary malnutrition and 1 (0.5%) case of Turner syndrome. In another study done by Bibi A et al, NVSS was found to be most common (36.5%) and GHD was found second common in 17.9 % of all 649 children with short stature.[14] In our study CDGP remained more common in boys 51(66.2%) out of total of 77 cases while FSS was common in girls, 39 (59.1%) out of 66 cases and same was observed in the study done by sultan M et al, where CDGP was found 31(83%) males out of total 37cases and FSS was in 20(66%) females out of total 32 cases.[15]

Mean mid-parental height in our study population was 161± 8 cm, while in another study done on short stature by Ullah F et al, mean MPH was 156.87±11.82 cm.[16] Mean father height was 167.4 ± 6.2 cm and mean mother height was 153.2 ± 6.3 cm. This shows that in Pakistan, the gender difference for evaluation of MPH is 14cm as compared to 13cm. In another study done by Khan WI et al in Pakistan, mean father height was 171.10±3.52cm and mean mother height was 154.39±4.56cm.[17] MPH is an important parameter for the evaluation of short stature and prediction of the final height according to Tanner-Whitehouse method.[11]

Most of the data in literature about the short stature shows that this idiopathic group of short stature has been included in the normal variants of short stature (CDGP and FSS).[18] But actually it's a different entity because there are so many unexplained cases of genetic short stature some of which has be found in recent studies like SHOX, PAPPA2, NPPC, NPR2, ACAN, PTPN11 (and other RASopathies), FBN1, BMP2 and IHH.[19] It is very important to know exactly the frequency of various causes of these genetic short statures from a given population in order to differentiate normal variants of growth from these pathologic genetic variant.

In our study, ISS is the 3rd most common cause for short stature after normal variants of short stature (NVSS) and growth hormone deficiency (GHD). In future, more studies on the frequency, identification of the idiopathic causes and unknown genetic variants without any skeletal deformity can be done. Moreover, response of growth hormone or IGF-1 on the individual new genetic variants is of worth to study to get the hope for the management of ISS. The shortcomings of our study are the failure to calculate the peak height velocity and to measure the age onset of puberty in patients of ISS. It was because of the fact that our study duration was short for measurement of these characteristics.

CONCLUSION

In the literature constitutional short stature and familial short stature have been classified as Idiopathic short stature. But in real sense idiopathic short stature is a category where there is not enough evidence for the reason leading to short stature. The newer genetic causes of short stature have developed insights for the mechanisms of growth failure. ISS is the diagnosis of exclusion. It's more common in females and in pre-pubertal age group. This group of patients among the short stature needs more focus for extensive studies to identify its genetic factors and moreover, to evaluate the response to human growth hormone to manage it in time before achieving the puberty.

Ethical Approval: *Submitted*
Conflict of Interest: *Authors declare no conflict of interest.*
Funding Source: *None*

REFERENCES

1. Polidori N, Castorani V, Mohn A, Chiarelli F. Deciphering short stature in children. Ann Pediar Endocrinol Metab. Jun 2020; 25(2): 69–79. doi: 10.6065/apem.2040064.032
2. Khan IVH, Harshini BP, Ashoka C, Kumar GV. Etiological Study of Short Stature among Children Attending Outpatient Department of Pediatrics in a Tertiary Care Medical College Hospital. Asian J Clin Pediatr Neonatol 2020; 8:32-36.

3. Almutairi RA. Short Stature in Children. Int J Diabetes Dev Ctries. Mar 2018; 2:9-15.
4. Mittal M, Gupta P, Kalra S,Bantwal G, MK. Short Stature: Understanding the Stature of Ethnicity in Height Determination. Indian J Endocrinol Metab. 2021 Sep-Oct 2021; 25(5): 381–388.
5. Jawa A, Riaz SH, Assir MZK, Afreen B, Riaz A, Akram J.Causes of short stature in Pakistani children found at an Endocrine Center. Pak J Med Sci. Nov – Dec 2016;32(6):1321-1325.
6. Hussein A, Farghaly H, Askar E etal. Etiological factors of short stature in children and adolescents: experience at a tertiary care hospital in Egypt. Therapeutic Advances in Endocrinology and Metabolism. May 2017; 8(5):75-80.
7. Singh H, Tiwari P, Bhavi V, Chaudhary PS, Suravajhala P, Mohan MK, Mathur SK. Application of Chromosomal Microarray for Evaluation of Idiopathic Short Stature in Asian Indian Children: A Pilot Study. Indian J Endocrinol Metab. Jan-Feb 2018;22(1):100-106
8. Hayden GF, Rogol AD. Etiologies and early diagnosis of short stature and growth failure in children and adolescents. J Pediatr. May 2014;164(5):1-14.
9. David A, Buts H, Halasz Z, etal. The prevalence of SHOX gene deletion in children with idiopathic short stature. A multicentric study. Orv Hetil. Aug 2017;158(34):1351-1356.
10. Inzaghi E, Reiter E, Cianfarani S. The Challenge of Defining and Investigating the Causes of Idiopathic Short Stature and Finding an Effective Therapy. Horm Res Paediatr. Oct 2019; 92(2): 71-83. .
11. Ostojic SM. Prediction of adult height by Tanner-Whitehouse method in young Caucasian male athletes. QJM. Apr 2013; 106(4):341-345.
12. Rohde A, Moszynska MO. Idiopathic short stature, current knowledge and perspectives – Review article. Pediatria Polska. May–June 2017; 92(3):303-308.
13. Al-Jurayyan NA, Mohamed SH, Hessah M, Al Otaibi HM, Al Issa ST,Omer HA. Short stature in children: Pattern and frequency in a pediatric clinic, Riyadh, Saudi Arabia. Sudan J Paediatr. 2012; 12(1):79-83.
14. Bibi A, Aamir M, Haroon ZH, Maqsood U, Hajira, Qamar U. Etiological study of short stature in children and role of insulin like growth factor-1 and insulin like growth factor binding protein-3 as screening markers for growth hormone deficiency. JPMA Feb 2023; 73 (2): 323-327.
15. Sultan M, Afzal M, Qureshi SM, etal. Etiology of short stature in children J Coll Physicians Surg Pak Aug 2008; 18(8):493-397.
16. Ullah F, Gaffar T, Afridi AK, Ali A, Aamir AH. Short stature: What is the cause in our population. J Ayub Med Coll Abottabad. Jan - Mar 2016; 28(1):135-140.
17. Khan WI, Noreen A, Tabasum S. Frequency of familial short stature identified in children presenting with short stature at a tertiary care hospital in Multan, Pakistan. Professional Med J. July 2021; 28(7): 993-996.
18. Rosenbloom AL. Idiopathic Short Stature: Conundrums of Definition and Treatment. Int J Pediatr Endocrinol. Mar 2009; 470378.
19. Jee YH, Baron J, Nilsson Ola. New developments in the genetic diagnosis of short stature. Curr Opin Pediatr. Aug 2018; 30(4):541-547.

AUTHOR'S CONTRIBUTIONS

MU: Designed Research Proposal, Data Collection, Manuscript Writing
SA: Statistical Data Analysis
ARC: SPSS Data Entry, Abstract Writing
AN: Discussion
RG: Manuscript, Data collection
TAB: Supervision, Manuscript Preparation