International Journal of Contemporary Pediatrics
Penugonda N et al. Int J Contemp Pediatr. 2020 Dec;7(12):2331-2338
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20205094

Original Research Article

A study of etiological and clinical profile of short stature in a tertiary care center

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Received: 06 October 2020
Accepted: 03 November 2020

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ABSTRACT

Background: Short stature is the common finding in pediatric endocrine practice with diverse etiology. However, compared to western world, data addressing the etiological and clinical profile of short stature in India are limited. The present study aimed to evaluate etiological and clinical profile of short stature in children. The primary objective was to identify children with short stature and evaluate various causes of short stature and secondary objective was to identify the gender and height differences among the different causes of short stature.
Methods: This prospective observational study analysed the data of 100 children aged 2-16 years, who presented to the department of paediatrics, Apollo Hospital, Chennai for the evaluation of short stature and poor growth during the period of April 2016 to April 2017.
Results: The predominant causes of short stature were growth hormone deficiency (GHD; 28%), normal variant short stature (26%), followed by chronic disease (8%), syndromic short stature (8%), Turner syndrome (7%), and hypothyroidism (6%). The most common causes of short stature in males were GHD (28%), constitutional delay of growth and puberty (CDGP; 24%) and familial short stature (FSS; 16%), whereas in females GHD (28%), Turner syndrome (14%) and FSS (12%). Beside this, 96% children had <3rd height centile and 4% children had >3rd height centile, of which 3 cases of GHD and 1 case of syndromic short stature were identified.
Conclusions: The most common causes of short stature identified in our study were GHD and normal variant short stature.

Keywords: Growth hormone deficiency, Normal variant short stature, Turner syndrome, Short stature, Constitutional delay in growth and puberty, Familial short stature

INTRODUCTION

Short stature is one of the common presentations in pediatric endocrine practice.[1] A child is considered to be short when his/her height is below the 3rd centile on height chart or more than 2 standard deviations (SD) below the corresponding mean height for the specific age, sex and race.[2,3] Short stature is a presenting symptom of diverse etiologies that ranges from normal variant short stature i.e. constitutional delay in growth and puberty (CDGP), and familial short stature (FSS) to pathological conditions like endocrinological disease example- growth hormone deficiency (GHD), chronic diseases, example- chronic renal failure, diseases of bone example- skeletal dysplasia or clinically defined syndrome.[1] So, early diagnosis and treatment of short of stature is most of the time rewarding and is imperative for the final outcome.

However, data addressing the etiology and clinical profile of short stature in India are limited. In this perspective, the

present study was undertaken to evaluate etiological and clinical profile of short stature in children between the ages of 2-16 years.

METHODS

A 1-year prospective observational study was conducted at the department of pediatrics, Apollo Hospitals, Chennai. Between April 2016 to April 2017, 100 children aged 2-16 years with short stature were identified and enrolled, if they met the inclusion and exclusion criteria.

Inclusion criteria

Children aged 2-16 years, with height more than 2 standard deviation (SD) below the mean for specific age and sex or height <3rd percentile; low growth velocity (<4 cm/year) or small for mid parental height (MPH) (difference of height SD score (HSDS) and MPHSDS ≤1.5).

Exclusion criteria

Children suffering from cerebral palsy and contractures or with deformities interfering with measurement of exact height or whose parents refused to enroll their child in the study.

Methodology

Written informed consent was obtained from the parents/guardians and assent was obtained from children before commencement of the study. Study was approved by institutional ethical committee (ECR/37/Inst/TN/2013 dated18 April 2016). A detailed history, including developmental history, history of systemic illness, social history, family history of short stature, age at puberty of each parent was noted.

Initial screening tests: hemoglobin, erythrocyte sedimentation rate, serum creatinine, serum alanine aminotransferase, free thyroxine (T4) and thyroid stimulating hormone, serum insulin like growth factor 1 levels were done in all children. Additional investigations like screening for celiac disease, arterial blood gas, follicle-stimulating hormone, karyotyping and further testing based on history and clinical examination were done on a case-to-case basis. In children with suspected GHD, GH stimulation tests with clonidine/glucagon were done. MRI of brain and sella were done for confirming GHD. Bone age estimation was done by doing x ray of the left hand with wrist by Greulich and Pyle method.

Children also underwent complete anthropometric examination, including height, weight, body mass index (BMI), upper segment-lower segment ratio, MPH and thorough clinical examination for pallor, dysmorphism, disproportion, hypertension, goiter coarse skin, central obesity, striae, cardiac murmur, mental retardation, midline defects, micropenis including puberty staging and data was entered into a pre-designed study pro forma.

Primary and secondary endpoints

The primary end point of the study was to identify children with short stature and evaluate various causes of short stature. The secondary end point was to identify the gender and height differences among the different causes of short stature.

Statistical analysis

All the continuous variables were assessed for normality using a Shapiro Wilk's test. If the variables follow normal distribution, they were expressed as mean±SD otherwise median (inter quartile range). All other categorical variables were expressed either as percentage or proportion. Comparison of normally distributed continuous variables was done by independent sample 't' test or analysis of variance (ANOVA) based on the number of observations. Comparison of categorical variables was done by chi-square test or Fisher's exact test based on the number of observations. Data entry was done by Microsoft (MS) excel spreadsheet. Data validation and analysis was carried out by statistical package for the social sciences (SPSS) version 16.0. All p values <0.05 were considered as statistically significant.

RESULTS

Frequency of various causes of short stature

The frequencies of various causes of short stature in this study are shown in (Figure 1). The predominant causes of short stature were GHD (28%), normal variant short stature (26%), followed by chronic disease and syndromic short stature each contributing to (8%), Turner syndrome (7%), and hypothyroidism (6%). The other causes that contributed for short stature in our study included small for gestational age (SGA) nutritional deficiency, Down syndrome, precocious puberty, idiopathic short stature (ISS), rickets and skeletal dysplasia. Five cases remained undiagnosed as they did not undergo a complete evaluation.

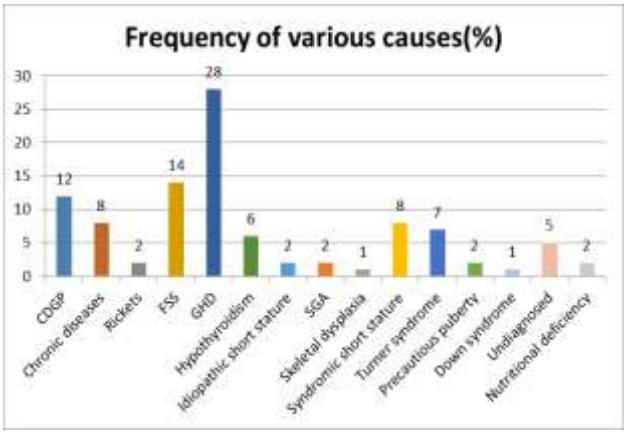

Figure 1: Frequency (%) of various causes of short stature.

Analysis of major causes of short stature

Among 28 cases of GHD, 60.7% children had isolated GHD, 28.6% had hypopituitarism, 7.1% had pituitary tumors, of which one had pituitary adenoma and one had pilocytic astrocytoma, 3.6% had acquired hypopituitarism due to secondary hemosiderosis (Figure 2). Among 25 cases of isolated GHD and panhypopituitarism, 9 cases had abnormal MRI findings.

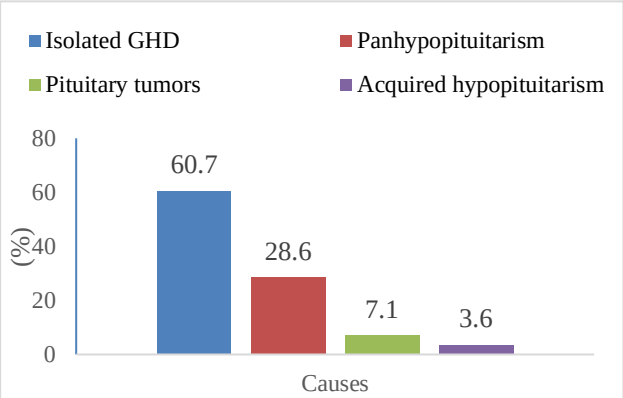

Figure 2: Causes of short stature in GHD.

In 8 cases of syndromic short stature, the following syndromes were observed: Albright hereditary osteodystrophy with pseudohypoparathyroidism, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, chromosome 9p duplication syndrome, Meier Gorlin syndrome, Job syndrome and three children had undefined syndromic short stature.

Out of 8 cases of short stature due to chronic disease, two children had Crohn's disease, one child had chronic kidney disease, one child had Barter syndrome, one child had type 1 diabetes mellitus and three children had chronic anemia's including sickle cell anemia, hemoglobin E (HbE) beta thalassemia, and Fanconi anemia. In 7 cases of Turner syndrome, 5 children had karyotyping of 45, x and two children had mosaic cerotype 45, x/46xx. In 6 cases of hypothyroidism, three children had congenital hypothyroidism. Among the cases of congenital hypothyroidism one child had thyroid agenesis and two children had ectopic thyroid which was grossly hypo functioning.

Demographic variables among various causes of short stature

Age and gender distribution

In our study, 13% of the children were in the age group of 2-5 years, 40% were in the age group of 5-11 years and 47% were in the age group of 11-16 years. The most common age group observed in our study was 11-16 years (47%). FSS and GHD were the most common causes of short stature among the age group of 2-11 years. Interestingly, all the cases of skeletal dysplasia and Down syndrome were identified only in the age group of 2-5 years (Table 1).

Table 1: The knowledge about symptoms of rabies among the study population (n=52).

Diagnosis	Age group (years)					
	2-5		5-11		11-16	
	% within age	% within diagnosis	% within age	% within diagnosis	% within age	% within diagnosis
CDGP	0	0	5	16.7	21.3	83.3
Chronic diseases	0	0	7.5	37.5	10.6	62.5
Rickets	7.7	50	0	0	2.1	50
FSS	23.1	21.4	17.5	50	8.5	28.6
GHD	15.4	7.1	32.5	46.4	27.7	46.4
Hypothyroidism	7.7	16.7	10	66.7	2.1	16.7
ISS	0	0	0	0	4.3	100
SGA	7.7	50	0	0	2.1	50
Skeletal dysplasia	7.7	100	0	0	0	0
Syndromic short stature	7.7	12.5	10	50	6.4	37.5
Turner syndrome	0	0	5	28.6	10.6	71.4
Precocious puberty	0	0	0	0	4.3	100
Down syndrome	7.7	100	0	0	0	0
Undiagnosed	15.4	40	7.5	60	0	0
Nutritional deficiency	0	0	5	100	0	0

The mean age of presentation of our study population was 10.1±4.1 years, of which mean age of presentation for male children was 11.2±3.5 years and for female children was 9.4±3.8 years. Mean age of first observation of short stature noted by parents of our study population was 6.5±3.7 years. Short stature was early recognized by the parents among the children with skeletal dysplasia, Down syndrome, SGA, hypothyroidism and FSS.

Our study had male to female ratio of 1:1. The most common causes of short stature in males were GHD (28%), followed by CDGP (24%) and FSS (16%), whereas in females most common causes of short stature were GHD (28%) followed by Turner syndrome (14%) and FSS (12%). Notably, all the cases of CDGP and Down syndrome were identified only in males and all the cases of ISS, SGA, skeletal dysplasia and Turner syndrome and precocious puberty were identified in females. Rickets, GHD, syndromic short stature and nutritional deficiency were equally distributed among males and females (Figure 3).

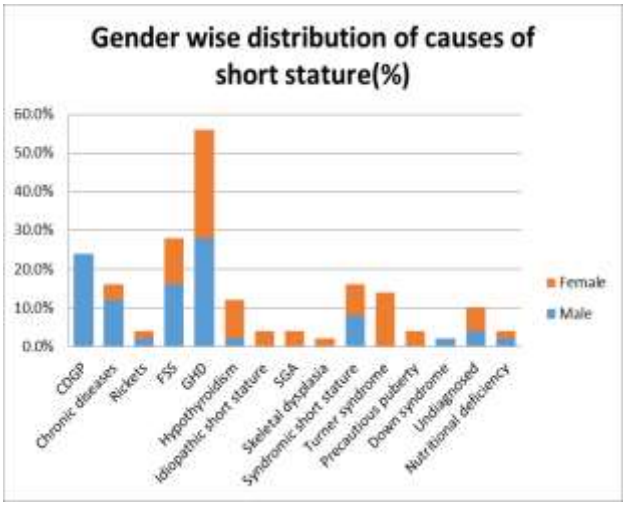

Figure 3: Gender distribution of various cause of short stature.

Term/preterm distribution

Out of total 100 children, 86% were term and 14% were preterm. The predominant cause of short stature among preterm children was GHD, FSS, CDGP and syndromic short stature (Table 2).

SGA/AGA/LGA distribution

Out of 100 children in our study, 18% were SGA, 80% were appropriate for age (AGA), 2% were large for age (LGA). GHD, FSS and SGA were the most common causes of short stature among the SGA. GHD, CDGP, syndromic short stature and Turner syndrome were identified as common causes of short stature in AGA. CDGP and chronic diseases were the only causes identified in LGA.

Family history of CDGP

In our study population, 19% cases of short stature had positive family history of constitutional growth delay. GHD, CDGP, FSS and Turner syndrome the most common causes of short stature among the children with family history of constitutional growth delay.

Pubertal staging

Most children of short stature were in pre pubertal staging (79%). Among the children in prepubertal staging, GHD, FSS, CDGP and Turner syndrome were the most common causes. Whereas among children who entered puberty, FSS, CDGP and GHD were the most common causes of short stature.

Comparative analysis of demographic variables of major causes of short stature

We further did the comparative analysis of the demographic variables of major causes of short stature, as presented in (Table 3).

Table 2: Term/preterm distribution of various causes of short stature.

Diagnosis	Gestation			
	Term		Preterm	
	% within gestation	% within diagnosis	% within gestation	% within diagnosis
CDGP	11.6	83.3	14.3	16.7
Chronic diseases	9.3	100	0	0
Rickets	2.3	100	0	0
FSS	14	85.7	14.3	14.3
GHD	26.7	82.1	35.7	17.9
Hypothyroidism	7	100	0	0
ISS	2.3	100	0	0
SGA	1.2	50	7.1	50
Skeletal dysplasia	1.2	100	0	0
Syndromic short stature	7	75	14.3	25
Turner syndrome	7	85.7	7.1	14.3
Precocious puberty	2.3	100	0	0
Down syndrome	1.2	100	0	0
Undiagnosed	4.7	80	7.1	20
Nutritional deficiency	2.3	100	0	0

Table 3: Analysis of demographic variables of major causes of short stature.

Demographic variables	CDGP	FSS	GHD	Hypothyr-oidism	Syndromic short stature	Turner syndrome
Mean age±SD (P value=0.06)	12.2±3.08	8.5±3.8	10.5±3.6	8.8±3.3	9.6±4.2	12.7±3.5
Mean age at first observation±SD (P value=0.05)	8.8±3.5	6.0±3.5	6.9±3.3	3.6±3.3	5.5±3.7	8.3±4.7
Gender (P value=0.01)% within diagnosis						
Male	100	57.1	50	16.7	50	0
Female	0	42.9	50	83.3	50	100
Gestation (P value=0.88)% within diagnosis						
Term	83.3	85.7	82.1	100	75	85.7
Preterm	16.7	14.3	17.9	0	25	14.3
Weight for gestation (P value=0.52)% within diagnosis						
SGA	0	14.3	25	16.7	12.5	14.3
AGA	91.7	85.7	75	83.3	87.5	85.7
LGA	8.3	0	0	0	0	0
Family history of CDGP (P value=0.33)% within diagnosis						
Yes	33.3	14.3	21.4	0	0	28.6
No	66.7	85.7	78.6	100	100	71.4
Puberty staging (P value=0.18)% within diagnosis						
Prepubertal	58.3	92.9	82.1	66.7	75	0
Pubertal	41.7	7.1	17.9	33.3	25	100

Anthropometric variables among various causes of short stature

Weight centile

In our study 53% of cases were in <3rd centile, 19% in 3-10 centile, 13% in 10-25 centile, 12% in 25-50 centile, 2% in 50-75 centile and 1% in 90-97 centile. The majority of children of <3rd centile belonged to GHD, CDGP, FSS and chronic diseases. All the cases of SGA, nutritional deficiency, skeletal dysplasia and Down syndrome were identified in <3rd centile group. Among the children with >50th weight centile, only Turner syndrome and hypothyroidism were noted.

Height centile

96% children had <3rd height centile, 4% children had height centile as >3rd centile. In children with <3rd height centile majority of cases were contributed by GHD (26%) followed by FSS (15%), syndromic short stature (7.3%) and Turner syndrome (7.3%). In children with height centile >3rd centile 3 cases of GHD and 1 case of syndromic short stature were identified, and they had a significant height deficit when compared to mid parental height. Hence, these cases were included under the study.

BMI centile

Among 100 cases of short stature, 12% cases were in <3rd centile, 12% in 3-5 centile, 5% in 5-10 centile, 19% in 10-25 centile, 10% in 25-50 centile and 29% in >50th centile. Among the cases in >50th centile majority of causes were contributed by GHD, Turner syndrome, FSS and hypothyroidism. Among children of <5 years, the majority of them were belonging to 3-50th weight for height centile. Children with GHD, CDGP and FSS were represented in all the BMI percentile groups.

Mean HSDS and difference of HSDS and MPHSDS

96% children had HSDS of ≤2, 4% children had HSDS of ≥2, of which 3 cases of GHD and 1 case of syndromic short stature were identified, but the difference in HSDS compared to MPHSDS was ≤1.5 for these children, hence included under the study. Mean HSDS of the study population was -2.9 1±0.98. Extremely short SDS ≤3 was observed in children of GHD, hypothyroidism, rickets, Turner syndrome, Down syndrome and for undiagnosed cases. The mean value of the difference of HSDS compared to MPHSDS was -2.06±1.23. The difference of HSDS compared to MPHSDS was within -1.5 for familial short stature cases. The midparental height of children with nutritional short stature was also short which suggest coexisting familial cause of short stature.

Distribution of HSDS among all children of short stature

Among 100 cases of short stature HSDS of 96% cases was ≤2 and of 4% cases was between -1 and -2. The majority of children had HSDS between -2 to -2.5 (Figure 4).

Comparative analysis of anthropometric variables of major causes of short stature

The comparative analysis of the anthropometric variables of major causes of short stature in our study are as listed in (Table 4).

Table 4: Analysis of anthropometric variables of major causes of short stature.

Anthropometric variables	CDGP	FSS	GHD	Hypothyroidism	Syndromic short stature	Turner syndrome
Weight centile (p value=0.01) % within diagnosis						
<3	66.7	57.1	39.3	50	37.5	28.6
3-10	8.3	21.4	28.6	16.7	25	14.3
10-25	16.7	21.4	17.9	0	12.5	0
25-50	8.3	0	14.3	16.7	25	28.6
50-75	0	0	0	0	0	28.6
75-90	0	0	0	0	0	0
90-97	0	0	0	1.7	0	0
Height centile (p value=0.84)% within diagnosis						
<3	100	100	89.3	100	87.5	100
3-10	0	0	7.1	0	12.5	0
10-25	0	0	3.6	0	0	0
Weight for height percentile (p value=0.610)% within diagnosis						
1-3	0	7.1	0	0	0	0
3-50	0	14.3	7.1	16.7	0	0
50-99	0	0	0	0	12.5	0
BMI centile (p value=0.610)% within diagnosis						
<3	8.3	7.1	14.3	16.7	12.5	0
3-10	33.3	7.1	3.6	0	12.5	14.3
5-10	8.3	14.3	3.6	0	0	14.3
10-25	16.7	14.3	25	16.7	12.5	0
Mean HT SDS±SD and mean difference SDS±SD						
Mean HT SDS±SD (P value=0.2)	-2.46±0.47	-2.43±0.30	-3.13±1.36	-3.16±1.03	-2.83±0.62	-3.03±0.98
MPH SDS±SD (P value=0.001)	-0.86±0.61	-1.52±0.50	-0.45±0.77	-0.88±0.69	-0.62±0.75	-0.58±0.65
Mean diff SDS±SD (P value=0.00)	-1.60±0.75	-0.90±0.53	-2.71±1.43	-2.28±1.23	-2.21±0.90	-2.45±1.11

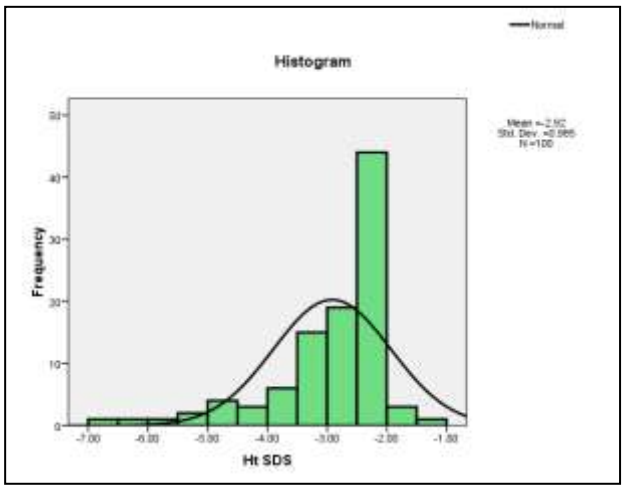

Figure 4: Distribution of HSDS of study population.

DISCUSSION

Growth assessment is an essential parameter in child care. Short stature can be promptly recognized with accurate measurement of growth and analysis of growth chart.[2,3]

In our study 100 children of short stature were analyzed of which 50% were males and 50% were females. Our data suggest short stature does not show gender preference. The commonest cause of short stature in our study was GHD (28%) followed by normal variant short stature (26%). Together they made up 54% of our diagnosis. In other studies, we noted the largest representation of diagnosis was with normal variant short stature.[4-7] The mean age of presentation of our study population was 10.1±4.1 years. In study by Dutta et al mean age of presentation was 11.34±3.71 years, whereas a study by Rabbani et al reported younger age group at the presentation.[5,8] The late presentation of short stature to our tertiary service suggests that there is a delay in identifying the problem, and the need for better pervasive screening of children for anthropometric problems from a younger age.

Out of 28% of children who had GHD in our study, 50% were males and 50% were females. A similar observation was made by Rabbani, et al in their study among 10.7% of children with GHD, 44.4% were males and 55.6% were females.[8] Whereas Lashari et al found that between 13%

of children with GHD, 69.2% were males and 30.8% were females.[6]

Among normal variant short stature 12% children were of CDGP and all were males. Mean age observed was 12.2±3.08. Song et al in their study observed mean age of CDGP was 8.23±3.63 and among 17.7% children of CDGP, 60.3% were males and 39.7% were females.[9] According to Dutta et al mean age of CDGP in their study was 12.31±2.54.[5] The male preponderance in our study for CDGP was not replicated in other studies.

We had 2% of our cohort who had SGA as a cause for short stature. SGA is considered as an important cause of short stature, especially if affected children did not catch up by two years.[10,11]

In our study, HSDS of various causes was CDGP -2.46±0.47, FSS -2.43±0.30, GHD -3.13±1.36, hypothyroidism -3.16±1.03. A similar observation was made by Singh et al where the scores for CDGP was - 2.58, FSS -2.53, GHD -3.77, and hypothyroidism -3.53.[12] The heights of children with pathological short stature like GHD, hypothyroidism, rickets, Down syndrome, Turner syndrome and of unclassified were shorter (i.e. HSDS of ≤-3) than those for normal variant short stature (i.e. HSDS of ≥-3). These results were comparable with the previous studies conducted by Song et al and Papadimitriou et al.[9,13]

In our study, the frequency of turner syndrome was 7%, and it was the second most common cause in females. Our results are in agreement with the study of Song et al where 9.3% females had Turner syndrome.[9] Also, in a study by Bhadada et al the frequency of Turner syndrome observed was 7.4%.[4] A higher frequency of Turner syndrome in our cohort suggests a referral bias as compared to the incidence of this condition in the general population, but was similar to findings in other studies in this subject.

An interesting feature of our study was the contribution made by syndromic short stature as the cause of short stature. It forms a small but significant diagnosis in our cohort, thereby suggesting a formal genetic work up and referral would be prudent when the diagnosis is not clear in initial screening for this short stature.

Limitations of the study

Few limitations of our study were the small sample size and it was conducted at a tertiary care center, so the study population may not reflect the general population. Also, failure to calculate and plot growth velocity that requires a regular follow up at 6-12 month interval was not possible, as the duration of our study was one year.

CONCLUSION

The etiological spectrum of short stature varies from center to center depending on the patient referred for short stature. The most common cause of short stature identified was GHD followed by normal variant short stature. Frequency of GHD was high in our study as the study was conducted at endocrine department where the patients were referred for growth failure. Turner syndrome was the second most common cause of short stature among females. This study can also serve as baseline data for further research and work.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Miller BS, Zimmerman D. Idiopathic short stature in children. Pediatric Ann. 2004;33:177-81.
2. Kamboj M. Short stature and growth hormone. Indian J Pediatr. 2005;72:149-57.
3. Khadilkar V, Yadavas S, Agawam KK, Tambala S, Banerjee M, Cherian A, et al., Revised IAP growth charts for height, weight and body mass index for 5- to 18-year-old Indian children. Ind Pediatr. 2015;52:47-55.
4. Bhadada SK, Agrawal NK, Singh SK, Agrawal JK. Etiological Profile of Short Stature. Indian J Pediatr. 2003;70(7):545-7.
5. Dutta D, Biswas K, Arora R, Barman N, Bhushan D, Bhakhri BK. Profile and Height Outcomes of Children with Short Stature in North India: An Experience from a Tertiary Care Centre. Ind J Pediatr. 2014;81(2):205-6.
6. Lashari SK, Korero HB, Memo 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.
7. Sultan M, Afzal M, Qurush SM, Aziz S, Lotmullah M, Khan SA, et al. Etiology of short stature in children. J Coll Physicians Surg Pak. 2008;18(8):493-7.
8. Rabbani MW, Khan WI, Afzal AB, 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.
9. Song KC, Jin SL, Kwon AR, Chae HW, Ahn JM, Kim DH. Etiologies of short stature. Ann Pediatric Endocrinol Metab. 2015;20:34-9.
10. Coutant R, Carel JC, Letrait M, Bouvattier C, Chatelain P, Coste J, et al. Short stature associated with intrauterine growth retardation, final height of untreated and growth hormone-treated children. J Clin Endocrinol Metab. 1998;83(4):1070-4.
11. Abuzzahab MJ, Schneider A, Goddard A, Grigorescu F, Lautier C, Keller E, et al. IGF-1 receptor mutations resulting in intrauterine and postnatal growth retardation. N Engl J Med. 2003;349:2211-22.
12. Singh P, Sharma PK, Agnihotri A. Coeliac disease in patients with short stature: a tertiary care centre experience. Natl Med J India 2015; 28: 176–180.

13. Papadimitriou A, Douros K, Papadimitriou DT, Kleanthous K, Karapanou O, Fretzayas A. Characteristics of the short children referred to an academic paediatric endocrine clinic in Greece. J Paediatr Child Health. 2012;48:263-7.

Cite this article as: Penugonda N, Selvarajan R, Ramakrishnan B. A study of etiological and clinical profile of short stature in a tertiary care center. Int J Contemp Pediatr 2020;7:2331-8.