

## Research Paper

## Causes of Short Stature in Children Referred to a Tertiary Care Center in Southeast of Iran: 2018-2020

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## ABSTRACT

**Background:** Short stature is a common problem encountered by endocrinologists. Short stature may be due to normal variations of growth or pathologic process. Evaluation of short stature and its causes in any community can be effective in reducing physical and mental illness in children.

**Objectives:** The objective of this study was to evaluate the frequency of common causes of short stature in children referring to the endocrinology clinic.

**Methods:** This prospective and descriptive study was carried out between August 2018 and September 2020. Included criteria were age below 18 years, height more than 2 SD below the mean for age (< 3rd percentile), growth failure (< 4 cm/year), small for mid-parental height, and adequate follow-up. They were evaluated by anthropometric measurements, biochemical panel, hormonal tests, radiological studies, and hormonal provocative tests.

**Results:** A total of 509 cases, including 238 males (46.8%) and 271 females (53.2%) had short stature. The age of participants varied from 2-18 years. The mean chronological age was 11.83±3.44 years. Most study participants were over 10 years old (68%). Normal variants of growth with 271 (53.34%) children, were the most prevalent causes. These causes were in three subgroups: familial short stature: 133 (26.14%), constitutional delay of growth and puberty: 112 (22%), and idiopathic short stature: 26 (5.12%). Totally 238 cases (46.66%) were due to pathologic types of short stature. The leading cause of short stature in this group was growth hormone deficiency, which was seen in 70 (13.76%) patients.

**Conclusions:** The normal variants of short stature as a group were the most common cause of short stature, followed by endocrinological causes of short stature and non-endocrinological causes.

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## 1. Introduction

Growth is a tightly regulated process and is a basic intrinsic dimension of childhood health. The linear growth process can significantly be influenced by genetics but final adult height is influenced by external parameters, such as nutritional, hormonal, and environmental factors (1). Short stature is defined as height  $\geq 2$  Standard Deviations (SD) below the mean for children of the same age, sex, and racial-ethnic group or height below the 3rd centile (2).

Short stature may be due to normal variations of growth or pathologic process with the common reasons as follows: familial (genetic) short stature and delayed (constitutional) growth that are normal non-pathologic forms of growth. Idiopathic Short Stature (ISS) is a diagnosis of exclusion and is defined as a height below 2 SD of the mean age, with no endocrine, metabolic, or other pathological causes (3, 4). Idiopathic short stature is a kind of normal growth, but affected cases warrant monitoring regarding the possible undetected underlying disease. No treatment is needed for the normal variants of short stature, but the management of the emotional stress is required properly (5-8).

The subset of children with short stature has pathologic causes. Pathologic process may be due to chronic systemic disorders (renal, pulmonary, cardiac, and inflammatory bowel disorder), cancers, endocrine diseases (hypopituitarism, Growth Hormone (GH) deficiency, hypothyroidism, type 1 diabetes mellitus, Cushing syndrome, adrenal insufficiency, rickets), genetic disorders (cystic fibrosis, Celiac disease) and chromosomal disorders (Turners syndrome). Skeletal dysplasia, sexual precocity, malnutrition, and iatrogenic causes, such as chemotherapy, radiotherapy, glucocorticoids, and surgery can also contribute to short stature. Growth retardation is accompanied by small for gestational age and intra-uterine growth retardation (9-17).

In addition to the fact that a child's stature can be a sign of his or her physical health, short stature can also affect a child's mental health. Children with short stature are more at risk for psychiatric illnesses, like low self-esteem, educational problems, and social immaturity than others (17).

Therefore, evaluation of short stature and its causes in any community can be effective in reducing physical and mental illness in children. The prevalence of short stature and its underlying causes varies considerably in

different geographical areas, which can be justified by differences in the natural environment and social development (18-21).

Most studies in Iran about the causes of short stature have shown that normal growth variants are the most common reasons for short stature (22-25). However, due to the absence of studies on the causes of this problem in southeastern Iran, this study was performed on children referring to an endocrinology clinic affiliated with the Zahedan University of Medical Sciences.

## 2. Material and Methods

This prospective and descriptive research was conducted from August 2018 to September 2020 on all children/adolescents referring to an outpatient endocrinology clinic affiliated with Zahedan University of Medical Sciences for short stature. All children were residing in Zahedan, Southeast Iran. Included criteria were those aged lower than 18 years, the height of over 2 SD below the mean age (<3rd percentile), growth failure (<4 cm/year), small for mid-parental height, and proper follow-up (a minimum of 12 months). Subjects with kyphoscoliosis and contractures for whose height was not measurable were excluded.

Medical and growth history (antenatal, perinatal, and postnatal) was taken followed by physical examinations. All patients were examined by endocrinologists. Standing height (cm) was determined with no shoes or hat on a measurement device (Harpender Stadiometer), in accordance with the anthropometry techniques proposed by the WHO Child Growth Reference (2006) (26). The target height (cm) was determined according to the Tanner's approach (27) by the below equation: (father's height + (mother's height + 13))/2: boys, and ((father's height - 13) + mother's height)/2: girls. The lower segment was measured through standing height minus sitting height, the upper segment/lower segment was assessed from these assessments. We applied the Center for Health Statistics growth charts to determine the height Standard Deviation Score (SDS). The subjects' weight was determined by the Seca balance (decimal of kg). Puberty was evaluated in the age group of 11-15 years by assessment of breast development in girls, genital developments in boys, pubic and axillary hair growth in both sexes, according to Tanner's classification (28, 29).

Primary screening tests, including complete blood count, erythrocyte sedimentation rate, fasting plasma glucose, renal function test, electrolytes, liver function test, calcium, phosphorus, alkaline phosphatase, vita-

min D levels, FT4, TSH, serum Ig A, anti-tTGs, urinalysis, venous blood gas (Bicarbonate), and Insulin-Like Growth Factor I (IGF-I) were performed for all participants. GH Clonidine test was performed as needed. The patient was subjected to the second GH provocative examination using levodopa (if needed). For peripubertal cases, the appropriate sex steroids were applied for priming prior to the test. Growth hormone less than 7 µg/L was considered as GH deficiency.

Bone age was determined through radiological assessment (by a single observer) of the bones' epiphyseal maturation or morphology of the left hand/wrist, compared with Greulich-Pyle charts.

Those with increased anti-tTGs levels were approved by endoscopic duodenal biopsy. Female patients with marked short stature (height of over 3 SD below the mean) with unidentified cause, with/without other evidence of Turner's syndrome were subjected to the chromosomal test. Pituitary magnetic resonance imaging (MRI) was considered if pituitary hormone disorders were confirmed.

Growth aberrations in pediatrics were classified as normal variants of growth and pathologic short stature, including, non-endocrine and endocrine disorders. Normal variants of growth included a constitutional delay of growth and puberty (CDG) (proportionate short stature, normal growth velocity and delayed bone age, bone age equal to height age, both less than chronological age, delayed puberty in patients who were in pubertal age, often with a family history of delayed pubertal development, or late adolescent growth spurt), familial short stature (FSS): (proportionate short stature with a normal growth velocity, bone age equal to chronological age and both more than height age, and short mid-parental height) and idiopathic short stature (ISS) when no apparent medical cause can be identified (short stature, low growth velocity, and normal growth hormone response to provocative testing).

Pathologic causes of short stature were evaluated. Short stature due to chronic diseases was confirmed based on history, physical examination, and related paraclinical assessments. GH Deficiency (GHD) was approved in cases, for whom the peak GH level did not reach 10µg/L using two provocative examinations (30, 31). Primary hypothyroidism was defined with a low thyroxine and a high thyrotropin concentration, whereas central hypothyroidism was detected by a low thyroxine, and normal or low thyrotropin concentration. In cases of suspected renal tubular acidosis (RTA) and metabolic

acidosis, urinary and blood pH was assessed. Chromosomal studies were used to diagnose Turner's syndrome. Skeletal dysplasia was confirmed by a bone survey.

The Zahedan University Ethics Committee for Human Studies approved the protocol (Code: IR.ZAUMS.REC.1398.280). The patients or their parents/legal guardians signed the consent form.

### Statistical analysis

Continuous and categorical data are presented as Mean±SD and frequency (percentage), respectively. Using the descriptive statistics, the frequency of different reasons for short stature was calculated. The student's t-test was applied to compare variables. Chi-square and Fisher exact tests were employed to compare categorical variables. Statistical analysis was performed by SPSS software v. 20 (SPSS, Inc., Chicago, IL). A p-value < 0.05 was regarded as significant.

## 3. Results

A total of 509 cases, 238 males (46.8%), and 271 females (53.2%) were identified as having short stature (female/male: 1.14:1). The age of participants varied from 2-18 years. Figure 1 shows the age-related histograms of the subjects in the study.

Twenty subjects (3.90%) of the total study population were under five years old; 158 (31.04%) aged more than five and less than ten years, and 331 (65.06%) aged more than ten years. As shown in Figure 1, most study participants were over ten years old. The age difference between the groups was statistically significant (p-value: 0.01). Figure 2 represents the frequency distribution of age groups for all participants (girls and boys).

As shown in Table 1, the Mean±SD chronological age was 11.83±3.44 years, and the Mean±SD bone age was 11.16±5.66 years. The Mean±SD mid-parents height was 161.57±9.35 cm. The height SD-score for all children was -2.54±0.96 cm.

Table 2 indicates the frequency of different reasons for short stature. Two main etiological categories were identified: normal variants of growth and pathologic causes. The normal variant of growth (non-pathologic) with 271 (53.34%) children, were the most prevalent causes. These causes included in three subgroups: FSS: 133 (26.14%), CDG: 112 (22%), and ISS: 26 (5.12%). FSS was the major reason for non-pathologically short stature.

**Table 1.** Characteristics of the study population

Variables	Mean±SD		
	Boys (n=238)	Girls (n=271)	Total (n=509)
Chronological age (Y)	11.32±3.19	12.42±3.63	11.83±3.44
Height (cm)	129.81±16.21	135.98±17.90	132.70±17.28
Weight (kg)	31.10±11.25	33.65±12.90	32.29±12.11
Ht SDS	-2.54±1.09	-2.55±0.78	-2.54±0.96
Wt SDS	-0.25±3.83	-0.91±1.41	-0.56±2.97
Bone age	9.97±7.07	10.39±3.45	10.16±5.66
FHt	167.46±6.71	168.66±6.34	168.03±6.56
MHt	155.40±6.43	156.66±6.49	155.99±6.48
Midparental Ht	155.02±6.37	168.99±6.07	161.57±9.35

Data are expressed as the mean ± standard deviation.

*Journal of Pediatrics Review*

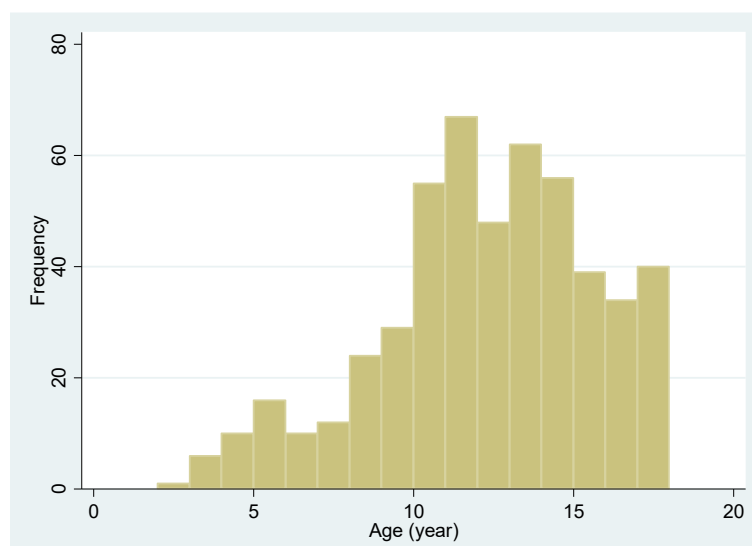
Ht SDS: Height Standard Deviation Score, Wt SDS: Weight Standard Deviation Score, FHT: Father Height, MHt: Mother Height.

Totally, 238 cases (46.66%) were due to pathologic types of short stature. The main etiology of short stature in this group was GHD (70 cases, 13.76%). In the children with isolated GHD, the mean Ht SDS was -3.2. In these subjects, the maximum GH response to provocative tests was 5.3 ng/ml. the second most common pathologic cause seen in these patients was hypothyroidism: 59 patients (11.59%). Vitamin D deficiency was seen in 381 (74.85%) cases that was usually combined with other endocrine disorders. Celiac disease was the cause of short stature in 37 (7.28%) cases. Twenty-two (4.34%) children were considered to have precocious puberty. Type 1 DM was found in 9 (1.77%) cases. Six

(1.17%) patients were found with panhypopituitarism as a cause of short stature. Other rare medical etiologies were Turner's syndrome, hypophosphatemic rickets, glucocorticoid use, autoimmune hepatitis, asthma, heart failure, and skeletal dysplasia.

#### 4. Discussion

The current study was conducted for the first time on 509 children and adolescents with short stature in southeastern Iran. FSS was found as the main cause of short stature (26.14%), and the second cause was CDG (22%). ISS accounted for 5.1% of all cases of short stat-

**Figure 1.** Age histogram of the study participants

*Journal of Pediatrics Review*

**Table 2.** Causes of short stature

Etiology	No. (%)		
	Male (n=238)	Female (n=271)	Total (n=509)
Familial short stature (FSS)	56(23.53)	77(28.42)	133(26.14)
Constitutional delay of growth and puberty (CDG)	74(31.09)	38(14.03)	112(22.00)
Idiopathic short stature (ISS)	12(5.04)	14(5.17)	26(5.12)
Growth hormone deficiency (GDH)	25(10.50)	45(16.24)	70(13.76)
Hypothyroidism	36(15.13)	23(8.49)	59(11.59)
Celiac disease	12(5.04)	25(9.23)	37(7.28)
Precocious puberty	2(0.84)	20(7.39)	22(4.34)
Renal tubular acidosis (RTA) Fanconi	7(2.95)	3(1.11)	10(1.98)
T1DM	5(2.10)	4(1.48)	9(1.77)
Panypopituitarism	1(0.42)	5(1.84)	6(1.17)
Turner's syndrome	1(0.42)	5(1.84)	6(1.17)
Hypophosphatemic Rickets	2(0.84)	1(0.37)	3(0.58)
Consumption of Glucocorticoids	1(0.42)	3(1.10)	4(0.78)
Autoimmune hepatitis	1(0.42)	2(0.73)	3(0.58)
Asthma	1(0.42)	2(0.73)	3(0.58)
Heart Failure	1(0.42)	2(0.73)	3(0.58)
Skeletal dysplasia	1(0.42)	2(0.73)	3(0.58)
Vitamin D deficiency*	183(76.9)	198(73.1)	381(74.85)

Journal of Pediatrics Review

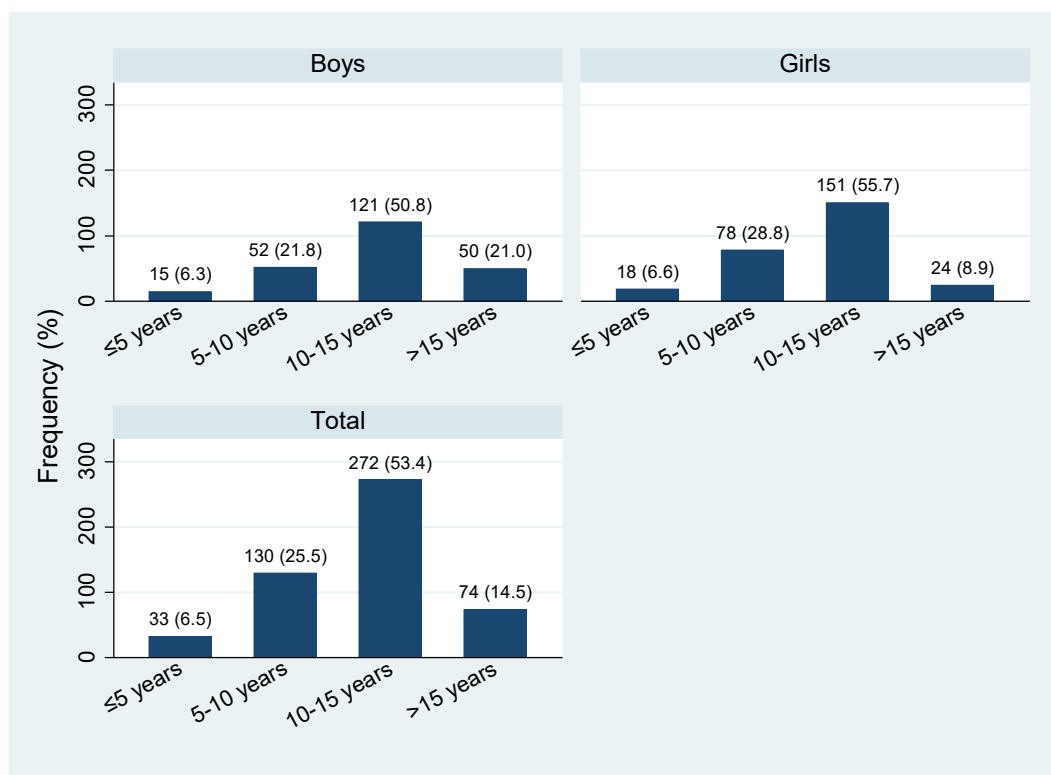
\* Vitamin D deficiency was seen in most subjects along with other abnormalities; thus, the sum of all these conditions does not correspond to the total number of patients.

ure. Thus, most patients with short stature (53.34%) were categorized in the non-pathologic group (FSS, CDG, and ISS).

The detected significance of normal variants of growth was in line with other studies in Iran and all over the world. For example, in a study conducted at the Tehran University of Medical Sciences, Iran, normal variants of growth, such as CDG and FSS were the commonest reasons for growth failure. In the study by Shiva et al., which was performed in Iran, normal variants of short stature were more than half of the causes of short stature. In another study conducted by Nakhjavani in Iran, constitutional growth delay and familial short stature were the most common causes of short stature (21-25, 32-34).

A similar observation was reported in a study by Rabani et al., in which FSS was the most common cause of short stature in Pakistani children (19). Gjokopulli et al. in Albani revealed CDG or FSS in 49.6% of short stature cases (21), which is consistent with other investigations, reporting short stature due to normal variants of growth (52-85%) (34-36). Thus, many subjects of short stature in children may be normal, as evidenced by accurate measurements, and determination of bone age with approved charts and expert radiological opinion. Early diagnosis of these cases is helpful in avoiding further and unessential studies and in alleviating the anxiety of the parents.

In our research, 46.66% of children with short stature were found with pathologic causes of growth retarda-



**Figure 2.** Distribution of age groups for all participants and girls and boys separately

Journal of Pediatrics Review

tion. Endocrinological causes were found in 73.13% of the cases, while nonendocrinologic causes were found with the frequency of 26.87% of all pathological causes of growth retardation.

We found GHD as the main endocrine cause of short stature (13.76%), while Moayeri et al. (22), Shiva et al. (25), and Gjokopulli et al. (21) have reported it as 23.4%, 6.1%, and 27.5%, respectively. Notably, our research was done in the endocrine referral centers; thus, it is expected to observe a high rate of endocrine diseases, particularly GHD. Also, to determine GHD, the health center situation, sampling, and sex steroids priming before GH provocative testing affecting its quality should be considered. The definition of GHD is controversial; however, the majority of experts regard a cut-off serum GH level of 10 ug/L (37). Most children with GHD were detected with idiopathic GHD, which is consistent with other studies.

Thyroid hormone is essential for bone development as well as linear growth in a child and its deficiency causes stunted growth and/or maturation arrest (38). Hypothyroidism was seen in 12% of cases in this study. Moayeri et al. (22) in Iran revealed short stature in 8% of their samples due to hypothyroidism, whereas it was 2.5% in the study by Shiva et al. (25) in Iran. The prevalence of

hypothyroidism was different from 1.4% to 17% in different global studies (19-21, 23).

Vitamin D is necessary for bone health and development in children; however, Vit D deficiency can be observed worldwide (39-41). Vit D deficiency has been announced in 90% of people in Zahedan, southeast Iran (42). We found Vit D deficiency (75%) as the main endocrine disorder in cases with short stature. It almost occurs with other endocrine reasons of short stature, which indicates this health issue in the general population.

Celiac was seen in 7.28% of cases in this study, whereas it was found to be 3.6% and 1.9% in research conducted by Jawa et al. (20) and Gjokopulli et al. (21). This percentage is higher than in other Iranian studies (22, 23). Celiac disease is not rare in Iran and its frequency in patients with short stature is about 33% (43).

The differences in the rate of different etiologies for short stature in studies may result from several parameters, such as genetics, socioeconomic status, nutrition, and other related parameters. Notably, the distribution of reasons for short stature in different populations to differentiate normal variants of short stature from the pathological causes that require early diagnosis and therapeutic interventions. Therefore, timely diagnosis



of treatable factors is effective to achieve a favorable long-term outcome.

The strengths of our study are the acceptable sample size and sufficient follow-up of patients for at least 12 months. The limitation of our study was limiting the research sample to an endocrine clinical referral center, which cannot provide the actual rate of causes in our population. Another limitation of our study was that the nutritional status of subjects was not evaluated, but we studied cases commonly in the upper/middle socioeconomic level. Studies using a larger sample size can provide more accurate estimations regarding the short stature causes and recognize potential causes.

## 5. Conclusion

The normal variants of short stature as a group were the most common cause of short stature, followed by endocrinological and non-endocrinological causes. Early recognition of these pathologies can be helpful in the achievement of normal height and improvement of quality of life. Further studies with a larger sample size can be a more accurate reflection of the short stature etiology distribution in our society.

## Ethical Considerations

### Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them.

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### Authors' contributions

Contributed to the design of the study and co-wrote the paper: Vahid Sheikhi; Contributed to the design of the study and co-wrote the paper: Shamim Bonyadi; Designed the study, performed bioinformatics analyses and wrote the paper: Zahra Heidari.

### Conflicts of interest

The authors of this article state that there are no conflicts of potential interest in conducting this research and its publication.

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