



## Etiology of short stature in children and adolescents

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### Abstract:

**Introduction:** Short stature is one of the most common causes of referral to the endocrinology and pediatric clinics and in most cases is due to normal variants of growth such as familial short stature or constitutional growth delay, but it may be due to some treatable and important diseases. In this study we investigate the causes of short stature in children and adolescents.

**Material and Method:** Every child or adolescent under 18 years old with height below 3rd percentile of growth charts, referred pediatric endocrinology clinic, included to the study. The height and weight of the children and their parents were measured and physical examination was done in order to find the cause of short stature. For all children a set of routine lab data performed. The left hand x-ray of each child was taken to determine the bone age and for evidences of bone dysplasia. Growth hormone stimulation test applied if there was any indication for this test.

**Result:** A total of 363 child and adolescent (173 male, 190 female) with short stature were studied. The more common causes of short stature included: familial short stature 39.9% (112 person), constitutional growth delay 26.4% (96 person), growth hormone deficiency 9.1% (34 person). The less common causes of short stature included: hypopituitarism , hypothyroidism ,

achondroplasia ,hypochondroplasia, Addison disease, cancer, chronic hepatitis, congenital ichthiosis, cystic fibrosis, cystinosis, Down syndrome and etc.

**Conclusion:** The most common cause of short stature in both sex was a normal variance followed by growth hormone deficiency. Less common but treatable causes should be always in differential diagnosis.

**Key words:** Short stature, Growth, Constitutional growth delay, Familial Short stature, Children

## **Introduction**

Growth is a complex process and can be influenced by genetic, endocrine system function, nutritional status, physical activity level, and chronic illness. In each of these cases, the disorder can lead to growth failure and short stature [1, 2]. Regular use of the growth chart is the key to detecting abnormal growth during infancy and childhood and begin preventive measures and treatment[2]. Short stature (SS) is one of the common causes of referrals to pediatric endocrinologists[2]. There are multiple definitions for short stature, defined as a height of more than two standard deviations below the mean for age and sex or as a height lower than third percentile[3-5]. Also a height lower than tenth percentile has been used as a definition for SS[6, 7]. The most common causes of SS included familial SS and constitutional growth delay, but a wide spectrum of the diseases can result to SS [1, 2]. Endocrine disorders such as hypothyroidism , hypopituitarism, Cushing syndrome, Addison disease and etc are relatively common and treatable causes of SS. Gastrointestinal disorders, chronic renal insufficiency, chronic anemia, inflammatory diseases , achondrodisplasia and chromosomal disorders such as turner syndrome also may present with SS[6, 8]. A careful history and physical examination can helps us to differentiate pathologic causes from normal variants, and prevents unnecessary evaluations. The availability of recombinant human growth hormone for improvement of final height increases desire for definite diagnosis and prediction of final height [9-11]. It is evident that the correct understanding of the etiology of short stature in any society can be a good guide for diagnostic and therapeutic policies. So, many endocrine centers attempted

to study the etiology of SS in their areas [6, 12, 13]. The aim of this study is to determine the causes of short stature in our area (Kashan / Iran).

## **MATERIALS AND METHODS**

This is a descriptive study that was conducted in 2013 in Kashan University of Medical Sciences. Non-random sampling method was used. The minimum required sample size of 350 was calculated. Any child or adolescent under 18 years with a height less than the 3rd percentile of standard growth curves published by the Centers for Disease Control and Prevention (CDC) have been enrolled. Data including age, gender, family history of short stature, history of chronic diseases such as bowel disease, malnutrition, celiac disease, and drug history from the parents or the child were obtained. The height and weight of the children and parents were measured. Measuring height in children less than 2 years of age performed by infantometer in recumbent position and in children above 2 years standing and by stadiometer with a maximum error of 0.1 cm. Measuring weight performed without shoes with a maximum error of 0.2 kg and measurements were carried out twice. The physical examination was performed to find the cause of short stature. Preliminary tests were performed for all children including CBC, thyroid function tests, electrolytes, urinalysis and creatinine. Other tests based on the suspected disorders were asked such as evaluation for celiac disease, cystic fibrosis (sweat test), and karyotype in cases of suspected chromosomal disorders. A left wrist and hand x-ray was performed for all cases to determine bone age and evidences of bone dysplasia. Standard deviation score (SDS) of height calculated with the formula:  $SDS = \frac{X - Y}{SD}$  where x=height, Y=mean height for age and sex, SDS=standard deviation score, respectively. GH stimulation test is requested for each of the following criteria [14, 15] :

- (1) If the patient's height is more than 3SD below the mean height for age and gender.
- (2) If the child growth velocity is less than 3 Percentile during the six-month follow-up.
- (3) A history of radiation therapy for head and neck
- (4) other evidences of hypopituitarism

Inclusion criteria: children younger than 18 years old with short stature (height below the 3rd percentile), and the desire to participate in the study. Exclusion criteria: No cooperation for required laboratory tests by the patient or the lack of time to measure growth velocity.

**Statistical analysis:** Statistical analysis was performed using SPSS, version 16.0 (SPSS

software Inc, Chicago, IL, USA). Values were presented as mean±standard deviation. P values lesser than 0.05(two-sided) were considered statistically significant. The Chi-square and T test were used for evaluation of differences between groups.

**Ethical Considerations:** Informed consent was obtained from all the children and their parents and they have been assured that their personal information is strictly confidential and the course of study does not impose additional costs to the patient. All participants have the right at any time if you plan to leave the study.

## **Results:**

**General Features:** In this study 363 children and adolescents under 18 years of age with short stature were included, the mean age was  $10.22 \pm 4.69$  years (173 male and 190 female) Average height of the study population was  $121.57 \pm 24.39$  cm and mean weight was  $27.24 \pm 14.23$  kg. General characteristics of the subjects were showed in Table 1. Height lower than 2SD were seen at 79.2% of individuals with familial short stature , 78.1% of constitutional growth delay and 86.7% of short stature due to growth hormone deficiency .

Height lower than 3SD (dwarfism) were seen in 9.2% of patients with familial short stature , 7.6% and 30% of constitutional growth delay and growth hormone deficiency, respectively. On the base of BMI, 296 patient (89%) had normal weight, 16 patients (4.8%) were overweight, 13 patients (3.9%) were obese, and 7 patients (2.1%) were underweight. Patients with constitutional growth delay had largest percentage of normal weights (93.3%), and patients with growth hormone deficiency had highest frequency of obesity and overweight (10% and 13.3% respectively) and there was a significant association between weight groups and the most common causes of short stature ( $P = 0.039$ ).

**Birth weight:** sixty seven cases (23.3%) had birth weight less than 2.5 kg (LBW) {33 male (23.9%) and 34 females (22.7%)}. History of LBW was present in 14% of patients with familial short stature, 16.7% of constitutional growth delay and 21.4% of growth hormone deficiency. A significant association was present between LBW history and familial short stature ( $P = 0.011$ ) but not with constitutional growth delay or growth hormone deficiency ( $P = 0.296$ ,  $P = 0.077$  respectively)

**Predicted adult height:** The highest average predicted adult height was related to the constitutional growth delay and lowest that one related to growth hormone deficiency.

Significant relationship between common causes of short stature and predicted adult height did not exist (P=0.164).

**Table 1: General characteristics of the subjects**

	Total		Male		Female		P value
	N	Mean± SD	N	Mean	N	Mean	
Age(yr)	363	10.22±4.69	173	10.44±5.05	190	10.02±4.35	NS
Weight(kg)	362	27.241±4.23	173	28.051±5.37	189	26.501±3.11	NS
Height(cm)	363	121.572±4.39	173	122.912±6.56	190	120.362±2.24	NS
Height-SDS	338	-2.61±.68	163	-2.62±.62	175	-2.59±.73	NS
BMI	362	17.05±4.63	173	17.00±4.14	189	17.09±5.06	NS
BMI-SDS	332	-.21±.87	161	-.24±.91	171	-.19±.83	NS
Birth weight	288	2.85±.61	138	2.89±.58	150	2.81±.63	NS
Birth height	164	47.79±3.07	73	48.04±.97	91	47.59±3.15	NS
Bone age(yr)	258	9.23±3.84	127	9.47±4.38	131	8.99±3.23	NS
PAH(cm)	167	15812±.08	79	167±9.40	88	149±6.96	<0.0001
Mother wt(kg)	345	65.1511±.94	165	65.7412±.46	180	64.6111±.45	NS
Mother ht(cm)	345	152.94±5.52	165	152.82±5.52	180	153.05±5.53	NS
Father wt(kg)	239	72.4012±.76	119	71.9312±.12	120	72.871±3.40	NS
Father ht(cm)	249	165.66±6.70	124	165.99±6.61	125	165.33±6.81	NS

SD: standard deviation, NS: not significant, BMI: Body mass index, BMI-SDS: Body mass index-standard deviation score, PAH: predicted adult height.

**Etiology of short stature:** Familial short stature was the most common cause of short stature (112 patient, 30.9%) followed by constitutional growth delay (96 patient, 26.4%). The most common cause of short stature in male subjects was constitutional growth delay and in females familial short stature (P< 0.0001). Third leading cause of short stature was growth hormone deficiency with the prevalence of 8% (6.4% of males and 9.5% of females). The combination of constitutional and familial short stature was seen at 1.9% of subjects. Etiology of short stature of the subjects was showed in Table 2 (for reasons of brevity, diseases with only one case not showed).

**Table 2: Classification of patients based on etiology of short stature and sex**

Etiology	Total		Male		Female	
	number	%	number	%	number	%
<b>Idiopathic :</b>						
<b>Familial short stature</b>	112	30.9	47	27.2	65	34.2
<b>constitutional GD</b>	96	26.4	67	38.7	29	15.3
<b>Constitutional GD &amp; Familial SS</b>	7	1.9	4	2.3	3	1.6
<b>SGA/LBW</b>	18	5.0	7	4	11	5.8
<b>Endocrine disorders:</b>						
<b>Isolated Growth hormone deficiency</b>	29	8.0	11	6.4	18	9.5
<b>Hypopituitarism</b>	4	1.1	2	1.2	2	1.1
<b>Hypothyroidism</b>	2	.6	2	1.2	0	0
<b>Syndromes:</b>						
<b>Down's syndrome</b>	8	2.2	3	1.7	5	2.6
<b>Noonan syndrome</b>	4	1.1	2	1.2	2	1.1
<b>Turner syndrome</b>	4	1.1	0	0	4	2.1
<b>Prader-willi syndrome</b>	2	.6	1	0.6	1	0.5
<b>Unknown syndromes</b>	7	1.9	2	1.2	5	2.6
<b>Bone dysplasia:</b>						
<b>Achondroplasia/hypochondroplasia</b>	3	.8	2	1.2	1	.5
<b>Pycnodysostosis</b>	2	0.6	1	0.6	1	0.5
<b>Inherited metabolic diseases:</b>						
<b>Mucopolysaccharidosis</b>	2	.6	2	1.2	0	0
<b>Other metabolic diseases</b>	5	1.4	1	0.6	4	2.1

**Less common causes:**

**Endocrine Disorders:** Panhypopituitarism, Addison disease, hypothyroidism. From the 4 patients with hypopituitarism in addition to growth hormone deficiency, two cases had diabetes insipidus, one case had hypogonadism and hypothyroidism and one case has been associated with hypogonadism. Two patients with growth hormone deficiency (a girl and a boy) had unknown syndrome. One patient with achondroplasia had also growth hormone deficiency.

**Metabolic disorders:** Niemann pick type C, cystinosis, phenylketoneuria, organic acidemia and mucopolysaccharidosiss.

**Gastrointestinal disorders:** chronic hepatitis, cystic fibrosis, ulcerative colitis with use of corticosteroids.

**Syndromes:** Down syndrome (most common), Noonan syndrome, Turner syndrome, Prader-willi syndrome and unknown syndromes.

**Dyschondroplasia:** achondroplasia and hypochondroplasia. One case of hypochondroplasia also had hypothyroidism.

**Renal causes:** chronic renal failure, nephrogenic diabetes insipidus.

**Other causes:** congenital ichthyosis, pycnodysostosis, cancer (ALL and medulloblastoma). The patients with familial short stature had maximum average height whereas the patients with growth hormone deficiency had the lowest average height.

**Etiology of short stature in different age groups:** Most common causes of short stature in different age groups included:

**0 to 2 years:** Short stature in a background of low birth weight (LBW) was the most common (n =12 , 44.4%) followed by the metabolic disorders and syndromes each of the 4 patients (14.8%).

**2 to 5 years:** Familial short stature (20.5 %), different syndromes (20.5 %), constitutional short stature (17.9%)

**5 to 10 years:** Constitutional growth delay (33%), familial short stature (27.2 %), growth hormone deficiency (8.8%)

**10 to 15 years:** Familial short stature (34.7%), constitutional growth delay (31.2%), growth hormone deficiency (9.7%)

**15 to 18 years:** Familial short stature (43.4%), constitutional growth delay (15.1%), growth hormone deficiency (7.6%)

There is significant relationship between the different age groups and etiology of short stature. (P <0.0001).

**Parental stature:** Average height of fathers was  $161.62 \pm 5.74$  cm in familial short stature,  $168.28 \pm 6.37$  in constitutional growth delay and  $164.95 \pm 5.58$  in short stature due to growth hormone deficiency (1 P <0.000), percent of fathers stunting was 66.2% , 23.9% and 30% respectively (P <0.0001). Short stature of mothers was seen in 50% of patients with familial short stature , 15.3% of constitutional growth delay and 25% of short stature due to growth hormone deficiency (P <0.0001). Short stature in both parents was seen in 65.4% of individuals with familial short stature, 38.2% of constitutional growth delay and 41.7% of short stature due to growth hormone deficiency (P <0.0001).

## Discussion

Short stature is the most common cause for referral to pediatric endocrinologists. Although most children with short stature are healthy and will have diagnose of normal variants (familial short stature and constitutional growth delay), it may be the only manifestation of an endocrine or systemic disorder. The objective of this study was to assess the etiology of short stature in children referred to pediatric endocrinology clinic. Short stature defined differently in researches [3-5]. More researchers considered the height more than 2SDS below mean for sex and age as a definition for short stature [16-18]. Sultan et al and Chowdhury et al considered criteria of height less than third percentile [12, 19]. Some researchers used criteria of height less than tenth percentile (height SDS < 1.2) for sex and age [6, 7]. Obviously if the used definition have narrower range, normal variants of growth (familial short stature and constitutional growth delay), would less detected and pathologic causes will have higher percentage of children with short stature. We studied, 363 children below 18 years old with height less than third percentile. The most of the other studies in Iran had lower number of cases and narrower range of age.[13, 20, 21]. In our study the most common cause of short stature was familial short stature in females (34.2%), and constitutional growth delay in males (38.7%), growth hormone deficiency in both sex lies in third place. Similar results achieved by sultan et al and Soheili Khah [19, 22] but Alaei et al reported in constitutional growth delay as the most common cause of short stature in both sex [13].In a tertiary medical center, most common cause of short stature was growth hormone deficiency and hypothyroidism in boys and chromosomal abnormalities and hypothyroidism in girls[12].



In subjects with age < 2 years, absence of growth spurt in infants with low birth weight (LBW) was the most common cause of short stature (44.4%), while in the age group of 2 to 5 years, familial short stature and syndromes were more prevalent. In children older than 5 years of age, normal variants of growth and then growth hormone deficiency were more common. In our study, normal variants of growth consisted about 68% of children with short stature (familial short stature 39.9%, constitutional growth delay 26.4% and constitutional & familial 1.9%). Normal variants of growth consisted about 85.5% of short stature cases in the Alaei et al. study and 65% in the study of Mohammedans et al.[13, 21]. In the study performed by Sultan et al., the most common causes were constitutional growth delay, familial short stature and malnutrition respectively. Also idiopathic short stature was most common cause of short stature in a recent study [1].Constitutional growth delay had a prevalence of 49%, 57% and 18% in other reports and familial short stature about 26.5% and 8% [12, 13, 21]. Pathological causes of short stature were responsible for 32% of cases in our study, and 35%, 14.5% and as high as to 82% in other reports [12, 13, 21]. Growth hormone deficiency is a quietly treatable cause of short stature in children and has a relatively high prevalence in our study (9.1% isolated growth hormone deficiency and 1.1% hypopituitarism). Growth hormone deficiency has been reported in other studies with a prevalence of 34.3% (Majcher et al, 2012), 15% (Chowdhury et al) and 30% (Mohammadian et al) [6, 12, 21]. An interest finding in our study was the association of two important cause of short stature in some cases such as hypothyroidism in a girl with achondroplasia and growth hormone deficiency in another girl with achondroplasia. In a study hypothyroidism as a cause of short stature was reported in 29% of cases [12] but in our experience the hypothyroidism was observed only in 2 cases (0.6%). Similar to our results has been reported by Shiva et al.(2.5% of 379 short children)[16]. A prevalence of 12% also has been reported[22]. The prevalence of chromosomal abnormalities in our work was relatively low (3.3%) and Down syndrome was the most common disorder followed by turner syndrome. A prevalence of 20% of chromosomal abnormalities in short stature children also has been reported [12].Turner syndrome were seen in 9.4% of 524 girls in a large sample research [6].

**Conclusions:** The most common cause of short stature in both sex was a normal variance followed by growth hormone deficiency. Less common but treatable causes should be always in differential diagnosis.

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