

## A PROSPECTIVE STUDY OF ETIOLOGY OF SHORT STATURE IN 426 SHORT CHILDREN AND ADOLESCENTS

Heshmat Moayeri,\* MD; and Yahya Aghighi, MD

Department of Pediatrics Endocrinology, Imam Khomeini Hospital, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran

**BACKGROUND**—Short stature is defined as subnormal height relative to other children of the same sex and age, taking family into consideration. This prospective study was designed in order to determine the etiologies of short stature with especial concern on the prevalence of growth hormone deficiency, and to compare the results with world-wide studies.

**MATERIALS AND METHODS**—We studied 426 subjects (272 boys and 154 girls) aged 4-18 years (mean,  $10.8 \pm 4.8$ ) with short stature. The decision to investigate the growth hormone axis was made with the knowledge that other explanations for growth failure have been excluded by documentation of a normal full blood count, ESR, renal function, and measurement of serum thyroxine concentration. In some female subjects, a karyotype was performed to exclude Turner's syndrome. Bone age was determined in all subjects.

**RESULTS**—Normal variants of growth including constitutional growth delay and familial short stature were identified as the most common causes of growth failure in this study. The results obtained in this study were in agreement with world-wide reports. Growth problems were more common in boys than in girls (1.8:1). Among the short subjects, 23.4% had classic growth hormone deficiency (GHD). Boys outnumbered girls 2:1 ( $p < 0.05$ ).

**CONCLUSION**—We conclude that (1) most children with short stature will not have an endocrine disorder, but in endocrine referral centers, the frequency of GHD is higher than in general clinics and (2) GHD appears to be more common in boys.

Keywords: constitutional growth delay; familial short stature; growth hormone deficiency; short stature.

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### INTRODUCTION

Growth is a continuous biologic process influenced by genetic, nutritional, environmental, and hormonal

factors. Normal growth can occur only if the individual is healthy.<sup>1</sup> Linear growth is generally considered to be decreased when a child's height falls more than 2 SD below the mean height for age, and when the patient's linear growth velocity diminishes to less than 4 cm/yr (child's growth shifts to a lower channel), or when the child is small for the midparental size.<sup>2-5</sup>

Health related causes of impaired linear growth include diverse systemic diseases, nutritional and emotional deprivation, endocrine diseases and a wide range of dysmorphic syndromes, inborn errors of metabolism, and chromosomal abnormalities.<sup>5-7</sup> Variants of normal growth including constitutional growth delay (CGD) and familial short stature (FSS) are the most common causes of short stature.<sup>1-4, 6,7</sup>

The majority of studies on subjects with short stature in Iran<sup>8-10</sup> indicate that variants of normal growth are the most common causes, but few have considered the characteristics of patients with growth hormone deficiency. The aim of this study was to determine the frequency of different causes of short stature with especial concern on the prevalence of growth hormone deficiency (GHD), and comparison of the results with world-wide studies.

### MATERIALS AND METHODS

A prospective and descriptive study was from October 1995 to October 2001. In this period, 564 children and adolescents with complaints of short stature were seen. The age of the 426 participants (272 males and 154 females) varied between 4 – 18 years (mean,  $10.8 \pm 4.8$ ). The subjects included in the study were based on the following inclusion criteria: (1) age below the 18 years; (2) height more than 2 SD below the mean ( $< 3^{\text{rd}}$  percentile), growth

\*Corresponding author:

Heshmat Moayeri, MD  
Department of Pediatrics Endocrinology  
Imam Khomeini Hospital, Tehran, Iran.  
Fax: +98-21-8270902  
E-mail: heshmat.moayeri@redsa.net

failure (< 4 cm/yr), or small for the midparental size; and (3) adequate follow-up (at least for six months). The exclusion criteria were: (1) height less than 2 SD below the mean (> 3<sup>rd</sup> percentile) with normal growth rate; (2) known severe somatic disease (e.g., rheumatoid arthritis or major thalassemia); and (3) inadequate follow-up.

All subjects were residents of Tehran and were referred to pediatrics endocrine clinics of Tehran University of Medical Sciences. All patients were examined by pediatric endocrinologists. An extensive health history was taken and a systemic physical examination was performed. Height and weight were measured and the stages of puberty were determined according to the classification of Marshall and Tanner. Standard deviation score (SDS) was measured in all subjects. Data were collected on age, sex, birth height, birth weight, parental heights, and the age of puberty for each parent. Primary screening tests including routine and complete blood count, ESR, renal function test, Ca, P, Alk. P, T4, TSH, stool exam, urinalysis, urine culture, and bone age radiographs were performed in all of the subjects. Bone age was determined by two pediatric radiologists. After excluding systemic diseases in euthyroid patients with pathologic short stature (height more than 3 SD below the mean) or slow growth rate (< 4 cm/yr), two provocative GH tests (L. dopa, clonidine, or insulin) were performed.<sup>11-17</sup>

Chromosomal study was performed in females with significant short stature (height more than 3 SD below the mean) and with unknown etiology, with or without other stigmata of Turner's syndrome.<sup>11</sup> Diagnosis of growth aberrations in children were grouped as: (1) normal variants of growth and (2) pathologic short stature including nonendocrine medical conditions, influencing growth and endocrine disorders. The pathologic group was divided into proportionate and disproportionated subgroups by assessing of the upper to lower segment ratio.

Normal variants of growth included CGD (i.e., proportionate small stature with a normal growth rate, delayed skeletal maturation often with a family history of delayed pubertal development, or late adolescent growth spurt) and FSS (i.e., proportionate short stature with a normal growth rate, skeletal age similar to chronologic age, absence of significant medical disorders, and short parents).

Nonendocrine systemic disorders were diagnosed by history, examination, and appropriately selected laboratory tests. Primary hypothyroidism was identified by a low thyroxine level and an elevated thyrotropin level, and central hypothyroidism was

diagnosed by a low thyroxine level, low T3 resin uptake and normal or low thyrotropin level. The diagnosis of Turner's syndrome was made by chromosomal study.

After excluding other causes of short stature, growth hormone deficiency was considered if a child had severely short stature (height more than 3 SD below the mean), a subnormal growth rate (a 1-year height velocity more than 1 SD below the mean) or height more than 1.5 SD below the midparental height (average of mother's and father's height), delayed bone maturation, and was confirmed if the peak growth hormone concentration failed to reach 10 ng/mL with two back to back provocative tests (L. dopa, clonidine or insulin).<sup>12,15,17,18</sup> A diagnosis of idiopathic short stature was considered in children with short stature, a subnormal growth rate, delayed bone age, no apparent medical cause for growth failure, and normal growth hormone response to provocative testing.<sup>6</sup> Skeletal dysplasia was confirmed by skeletal surveys.

### Statistical analysis

Statistical analysis was performed using SPSS version 9.4 (SPSS, Inc., Chicago, IL) for windows. We compared variables by using student's *t*-test. The values of *p* < 0.05 were considered to be statistically significant.

## RESULTS

Among 426 subjects that were diagnosed as having short stature, 201 (47%) had pathologic short stature and 225 (53%) had normal variants of growth. The frequency of different causes of short stature is shown in Table 1. Growth problems were more common in boys than in girls (1.8: 1). Constitutional growth delay 140 (33%), familial short stature 60 (14%), and isolated growth hormone deficiency 100 (23.4%) were the most common causes in this study. Thirty-four (8%) of children were considered to have hypothyroidism, 23 (5.4%) idiopathic short stature, 19 (4.5%) Turner's syndrome, 18 (4.2%) skeletal dysplasia, 15 (3.5%) panhypopituitarism, 11 (2.6%) systemic diseases, and 6 (1.4%) rickets.

Medical disorders reported included renal tubular acidosis, recurrent urinary tract infection due to vesicouretral reflux, chronic renal failure, chronic anemia, coeliac disease, and malnutrition. The characteristics of patients with GHD is shown in Table 2. Of the 100 children with isolated GHD, all but ten were at least 5 SD below the mean in height,

and growth rate ranged from 1.7 to 3.9 cm/yr (mean, 3.1 cm/yr). Ninety-six of children with GHD were considered to have idiopathic growth hormone deficiency after undergoing magnetic resonance imaging or computed tomography scanning. Four children had received surgery (3 for craniopharangioma and 1 for ependymoma).

In GHD children, boys outnumbered girls. In this survey, 28.6% of boys and 14.3% of girls with short stature were considered to have GHD. Most pubertal subjects were in stages I-II according to the classification of Marshall and Tanner [stage I: 145 (34%); stage II: 158 (37%), stage III: 69 (16%); and stage IV: 54 (13%)]. The mean of SDS, bone age, chronologic age, height age and growth velocity is shown in Table 3.

**Table 1.** Diagnosis of the 426 short children and adolescents, separated by gender.

Diagnosis	Boys No. (%)	Girls No. (%)	Total No. (%)
CGD	91 (33.4)	49 (31.9)	140 (33)
GHD	78 (28.6)	22 (14.3)	100 (23.4)
FSS	36 (13.2)	24 (15.6)	60 (14)
Hypothyroidism	20 (7.6)	14 (9)	34 (8)
ISS	14 (5.1)	9 (5.9)	23 (5.4)
Tumer's syndrome	—	19 (12.3)	19 (4.5)
Skeletal dysplasia	11 (4)	7 (4.5)	18 (4.2)
Panlypopituitarism	11 (4)	4 (2.6)	15 (3.5)
Systemic diseases	7 (2.6)	4 (2.6)	11 (2.6)
Rickets	4 (1.5)	2 (1.3)	6 (1.4)
Total	272 (100)	154 (100)	426 (100)

CGD = Constitutional growth delay; GHD = Growth hormone deficiency; FSS = Familial short stature; ISS = Idiopathic short stature.

**Table 2.** Characteristics by gender for short children with growth hormone deficiency (all data are presented as means  $\pm$  one standard deviation).

Characteristics	Male (No. = 78)	Female (No. = 22)
Age	14.1 $\pm$ 1.7	13.3 $\pm$ 2.1
Bone age	8.4 $\pm$ 2.9	7.2 $\pm$ 2.6
Height SDS	-5.9 $\pm$ 0.6	-6.7 $\pm$ 0.8
Growth rate (cm/yr)	3.4 $\pm$ 1.5	2.8 $\pm$ 1.2
Maximum stimulated GH (ng/mL)	5.6 $\pm$ 2.7	5.4 $\pm$ 2.5

## DISCUSSION

As growth is the essential biologic characteristic of childhood, failure of physical growth may be an important sign of diseases. Short stature may be a disability and a cause of distress in itself.<sup>6,7</sup> Therefore, short stature is important and requires

early assessment. In those cases needing treatment, such medical attention would be effective only before the epiphyses fuse. In present investigation and other studies that were performed in Iran,<sup>15, 16</sup> CGD, FSS, and GHD were the most frequent causes of short stature that are in agreement with worldwide studies.<sup>15, 19-21</sup>

It must be noticed that all of these studies were performed in the referral endocrine centers, therefore, the prevalence of endocrine disorders, especially GHD, was relatively high. In this study, 34.9% of the children with short stature had endocrine disorders, but in Utah study<sup>22</sup> and in a similar study that was performed in a group of elementary school children in Iran,<sup>10</sup> the large majority of students who were examined for short stature were found to have nonendocrine causes for growth failure, and the frequency of endocrine disorders were found to be less than 5%.

The large majority of children with GHD had idiopathic GHD, which is in agreement with other reports.<sup>19-21</sup> In this study, there was a significant difference in GHD prevalence between the genders, boys outnumbering girls (2:1). Other independent reviews on growth retardation revealed that boys outnumbered girls by 2.5: 1,<sup>19</sup> 2.7: 1<sup>22</sup> which is compatible with the results obtained in this study. The percentage of other diagnosis was remarkably similar for the two sexes. Thus it appears that GHD may be more common in boys.

Growth problems were more common in boys than in girls (1.8: 1). It is possible that this gender difference merely reflects greater parental concern about male height which leads to a self-referral ascertainment bias. As shown in Table 3, the least SDS and the slowest growth velocity are related to hypothyroidism and skeletal dysplasia, respectively and which are in agreement with other reports.<sup>19-21</sup> The most frequent, nonendocrine systemic disease, as the cause of short stature, was renal tubular acidosis which is similar to Zargar et al's study in Indian children,<sup>19</sup> but in other reports,<sup>20, 22, 23</sup> coeliac disease has been more frequent. In agreement with previous reports,<sup>7, 19, 22</sup> achondroplasia was the most frequent cause of disproportionate short stature in this study.

Thus, from a clinical point of view: (1) In general population, most children with short stature will not have GHD, and therefore caution should be used when one is interpreting the results of GH testing (the specificity and sensitivity of any tests of GH secretion is only 80%). So, the clinician should expect false positive and false negative results and that the therapeutic decision should not be based solely on these tests. (2) Determination of height

**Table 3.** The mean of SDS, bone age, chronological age, height age and growth velocity in 426 short children and adolescents.

Diagnosis	Mean of chronologic age	Mean of height age	Mean of bone age	Mean of SDS	Mean of growth velocity (cm/yr)
CGS	13.82	11.5	10.5	-2.8	5.9
GHD	13.75	7.5	7.8	-6.3	3.1
FSS	14.21	12.8	13.9	-2.5	6.2
Hypothyroidism	14.8	8.2	6.3	-7.8	1.95
ISS	13.41	8.26	7.9	-5.8	3.3
Turner's syndrome	15.34	9.8	10.1	-5.2	2.4
Skeletal dysplasia	4.9	1.9	2.5	-6.23	1.8
Panhypopituitarism	11.62	9.58	9.2	-6.82	2.8
Systemic diseases	11.23	7.8	8.1	-3.8	3.7
Rickets	5.41	3.2	2.8	-3.76	2.98

CGD = Constitutional growth delay; GHD = Growth hormone deficiency; FSS = Familial short stature; ISS = Idiopathic short stature; SDS = Standard deviation score.

velocity is the most critical factor in evaluating the growth of a child, therefore careful antropometric measurement (height and weight) needs to be made, recorded and plotted accurately on growth chart and decision making be based upon careful observation of growth and calculation of growth rate at an interval of not less than 6 months or preferably 12 months. In summary, the physician has three responsibilities in relation to short children: (1) to identify as early as possible those who may benefit from treatment; (2) to give an informed prognosis in order to reassure those who do not need treatment; and (3) to give practical advice to those who will be very short and can not be treated.

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