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# Etiological Spectrum of Childhood and Adolescent Short Stature at a Tertiary Care Hospital in Madurai, Southern India

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**Abstract:** ***Objectives: To assess etiological spectrum of short stature in childhood and adolescent patients and to study the prevalence of treatable causes of short stature like Growth hormone deficiency (GHD) and primary hypothyroidsm. Research Design & Methods: This descriptive cross sectional study; a stepwise diagnostic evaluation was done in 512 subjects of childhood and adolescent short stature, aged 3 -18 years attending Department of Endocrinology, Madurai Medical College, Madurai. All patients of short stature underwent detailed clinical, hematologic, metabolic and endocrine screening including thyroid function test and bone age estimation. Selected subset of patients subjected to whole body skeletal survey, blood karyotype and MRI pituitary. Growth hormone deficiency was diagnosed by peak GH levels <10 ng/ml following clonidine provocative test. Results: A total of 512 patients (M: F, 296:216) were recruited and mean age was 10.58 ± 3.65 years (Range 3-18 years). Familial short stature (FSS) and Constitutional growth delay (CGD) were identified as most common causes of short stature in this study, contributed 55% of short stature. Endocrine causes accounted for 15% of short stature [of them, 5.8% had growth hormone deficiency (GHD)], 9.3% had primary hypothyroidism]. Interestingly, syndromic causes including Down syndrome, Turners' syndrome and Prader Willi syndrome constituted 8.5% of children with short stature in our cohort. Conclusions: Constitutional growth delay (CGD) and Familial short stature (FSS) were the most common causes of short stature in this study. The treatable causes of short stature such as GHD, hypothyroidism, malnutrition and underlying chronic illnesses accounted for a considerable percentage of short stature. Periodic monitoring of growth and growth velocity with appropriate growth chart will help in early identifying the treatable causes of short stature.***

**Keywords:** Constitutional growth delay; familial short stature; growth hormone deficiency; short stature, primary hypothyroidism

## 1. Introduction

Short stature is defined as a height more than two standard deviations below the mean for age and sex (less than third percentile) [1]. It is one of the most common causes of referral to pediatric endocrinology clinics. The reported prevalence of short stature among different populations is between 2-8%[2]. The etiological spectrum of short stature varies between developing and developed countries because of differences in genetic factors, ethnicity, environmental, nutrition and socio economic status that affects growth[3].

Short stature is not a disease by itself and it may be the manifestation of several systemic or endocrine diseases like Growth hormone deficiency (GHD), primary hypothyroidism and Constitutional growth delay (CGD). Various syndromes like Down syndrome, Turners' syndrome, Prader Willi syndrome and Noonan syndrome are associated with short stature. Hence evaluating the underlying etiology of short stature is paramount importance, so that appropriated treatment can be initiated at an early stage before the epiphyseal fusion of bone. Growth hormone deficiency (GHD) and primary hypothyroidism are important treatable endocrine causes of pathological short stature[4]. Short stature associated with GHD has been estimated to occur in about 1/4,000 - 1/10,000 in various studies. A short child with no etiology is established is labelled as idiopathic short stature (ISS)[5].

Except one published from school going healthy children[6], no large studies are available in Southern India regarding etiological spectrum of short stature. Hence this study was aimed to assess etiological spectrum of short stature in childhood and adolescent patients as well as to study the prevalence of treatable causes of short stature like Growth hormone deficiency (GHD) and primary hypothyroidsm.

## 2. Research Design and Methods

This was a cross-sectional observational study to evaluate the etiological spectrum of short stature in patients attending Growth clinic. All short stature subjects attending the Growth clinic of Government Rajaji Hospital, Madurai Medical College over a period of three years from January 2016 to December 2018 were included in the study. Government Rajaji Hospital is a 2500 bed tertiary referral hospital for south Tamilnadu located in Madurai.

The inclusion criteria for the study were age between 3 and 18 years, height more than two standard deviations below the mean for age and sex (less than third percentile), growth velocity or height gain less than 4 cm/yr and/or small for the midparental height. The height of all children was measured by WHO approved stadiometer and plotted on the Khadilkar *et al*. growth chart[7].

A stepwise diagnostic evaluation was done in all 512 subjects. Patients were evaluated with detailed history including birth weight, consanguinity, nutritional status, socio economic status were documented. Puberty was determined by Marshall and Tanner grading, general and systemic examination including goitre and syndromic features were recorded. Initial screening tests was done in all patients which included complete blood count, renal function test, Calcium, Phosphorus, alkaline phosphatise ,TSH, Free T4, stool examination, urinalysis, and bone age

estimation. Selected subset of patients subjected to whole body skeletal survey, blood karyotype and MRI pituitary. Growth hormone deficiency was diagnosed by peak GH levels <10 ng/ml following clonidine provocative test. Primary hypothyroidism was diagnosed based on raised thyroid stimulating hormone (TSH > 10.0 mIU/mL) and low FT4 (<0.89 ng/dL) levels.

Based on the biochemical and radiological profile, Short stature was divided into two major groups as normal variants of growth and pathologic short stature. Normal growth variant group included CGD (i.e., proportionate short 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 that is proportionate short stature with normal growth rate, skeletal age similar to chronologic age in the absence of any systemic disorders. Data was analyzed by statistical package for social sciences (SPSS 10.0). The study was approved by the Institute Ethics committee of Madurai Medical College.

## 3. Results

The study sample consisted of 512 patients; out of them, 296 were male (57.81 %) and male:female ratio was 1.3:1, growth problems were more common in boys than girls. The frequency of different causes of short stature is shown in Table 1. Familial short stature (FSS) and Constitutional growth delay (CGD) were identified as most common causes (55 %) of short stature in this study. Non pathologic variant of short stature is summarized in Table 2. Endocrinological causes accounted for 15% of short stature [of them, 5.8% had growth hormone deficiency (GHD)], 9.3% had primary hypothyroidism]. Interestingly, syndromic causes including Down syndrome, Turners' syndrome and Prader Willi syndrome constituted 8.5 % of children with short stature in our cohort. Chronic illnesses contributed 9.3% of short stature that included renal tubular acidosis and chronic kidney diseases (25 patients), mal absorption related (5 patients) and haematological conditions like thalassemia and leukemia (18 patients). Achondroplasia, the most common cause of skeletal dysplasia constituting 2 percent of the total cases enrolled in the study.

## 4. Discussion

The stature or height has important role in individual's academic performances, occupation, sports participation and seeking marriage partners. Psycho-social distress is more common among family members with short stature. Hence paediatrician or family physician should assess whether child or adolescent is growing normal or any deviation. A detailed history along with anthropometric assessment is essential to suspect and diagnose the underlying cause. It is important to diagnose early and initiate treatment before the epiphyseal fusion.

The important causes of short stature in this study are familial short stature (40.62%) followed by constitutional delay in growth (14.25%). Hence the non pathological normal variants of growth constituted 55% of short stature children. Normal variant short stature constituted by FSS and CDG is far more common cause of short stature which needs to be reassured and followed up[3,4].

Pathological short stature comprises of smaller proportion of children requires detailed investigations and specific management. The prevalence of GHD in children with short stature varied between 2.8% to 40%[9]. In the present study GHD contributed 5.8% of short stature. Growth hormone therapy is a highly specific and targeted therapy which should be instituted under expert supervision; in our cohort 30 children were diagnosed to have GHD and on recombinant Growth hormone therapy.

Juvenile onset primary hypothyroidism is contributed 9.8% of short stature in the present study. Thyroid hormone receptors are situated in growth plate of growing child. Hence early identification of primary hypothyroidsm and initiation of levothyroxine therapy will be rewarding to treating physician with optimal height gain at very low cost.

Comparing with other published series of short stature from Indian subcontinent[3,4,9], our study cohort noted 8.5% of syndromic short stature including Down syndrome (5.8%), Turners' syndrome (1.6%) and Prader Willi syndrome (1.1%). Blood karyotype for Down and Turner Syndrome and methylation specific PCR method was used to confirm Prader Willi Gene in our cohort.

## 5. Conclusions

Familial short stature (FSS) and Constitutional growth delay (CGD) were the most common causes of short stature in this study. The treatable causes of short stature such as GHD, hypothyroidism, malnutrition and underlying chronic illnesses accounted for a considerable percentage of short stature. Periodic monitoring of growth and growth velocity with appropriate growth chart will help in early identifying the treatable causes of short stature.

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**Competing interest:** None

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**Table 1:** Etiological profile of the 512 subjects with short stature

| | All | Boys | Girls |
|---|---|---|---|
| Total subjects | 512 | 296 | 216 |
| Familial Short stature | 208 | 112 | 96 |
| Constitutional Growth delay | 73 | 61 | 12 |
| Idiopathic Short Stature | 10 | 7 | 3 |
| Small for Gestational Age | 11 | 6 | 5 |
| Growth Hormone Deficiency | 30 | 18 | 12 |
| Primary Hypothyroidism | 48 | 30 | 18 |
| Syndromes | | | |
| Down Syndrome | 30 | 13 | 17 |
| Turners Syndrome | 8 | 0 | 8 |
| Prader Willi Syndrome | 6 | 6 | 0 |
| Chronic Illnesses | | | |
| Malabsorption | 5 | 1 | 4 |
| Chronic Kidney Diseases | 25 | 16 | 9 |
| Haematological | 18 | 11 | 7 |
| Nutritional | 20 | 8 | 12 |
| Psychosocial | 10 | 3 | 7 |
| Skeletal Dysplasia | 10 | 6 | 4 |

**Table 2:** Non pathologic variant of Short Stature

| Etiology | N (%) |
|---|---|
| Familial short stature | 208 (40.62%) |
| Constitutional Growth delay | 73 (14.25%) |
| Idiopathic short stature | 10 (1.9% %) |
| Small for Gestational Age | 11 (2.1%) |