

Chapter 137

Short Stature: Evaluation and Management

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INTRODUCTION

Short stature is defined as height below 3rd centile or less than two standard deviations (SDs) below the median height for that age and sex according to the population standard; or even if the height is within the normal percentiles but growth velocity is consistently below 25th percentile over 6–12 months of observation.^{1,2} Approximately 3% children in any population will be short, amongst which half will be physiological (familial or constitutional) and half will be pathological.

Normal growth requires adequate nutrition along with various hormonal stimuli. The important hormones are: growth hormone (GH), insulin-like growth factor (IGF)-1, thyroid hormones, sex steroids and other growth factors. Linear growth is maximum during infancy; 25 cm in first year, 10 cm/year in next 2 years. Subsequently, it gradually declines to 6–7 cm/year till puberty when again growth accelerates in sigmoid manner when it is around 10 cm/year. Age of onset of puberty varies in different population and it correlates more with the bone age (BA) than chronological age (CA). Short stature could be due to constitutive intrinsic growth defect or because of any of the extrinsic factors which are required for normal growth.

INDIAN SCENARIO

The extent of problem and causes of short stature in Indian children is not precisely known. A study of child growth included 2,500 consecutive admissions to Bai Jerbai Wadia Hospital for Children in Bombay, India; 140 (5.6%) were considered to be of short stature (less than the 5th percentile of an Indian standard). The causes of growth retardation were in order of frequency: protein energy malnutrition (PEM) (42), chronic systemic disease (23), chronic anemia (19), skeletal disorders (16), constitutional short stature (15), endocrine disorders (15), intrauterine growth retardation (5), chromosomal disorders (2), and miscellaneous (3). All 10.7% of cases with endocrine problems had congenital hypothyroidism. In contrast, study of short stature among 430 children referred to the same hospital's endocrine clinic showed endocrine disorders was responsible for most short stature cases (143 or 33.3%). Ninety-seven of these cases (67.8%) had a deficiency of GH, while just 6.3% suffered from hypothyroidism. Malnutrition and chronic disease caused short stature in just 8.4%. In another study from Department of Endocrinology, Sher-i-Kashmir Institute of Medical Sciences, GH deficiency was the commonest identifiable cause of short stature and accounted for 22.8% of cases. Thirty-six subjects (18.7%) had a normal variant short stature. Renal tubular acidosis was diagnosed in 10.4%, primary hypothyroidism, malnutrition and hypothalamic syndrome in 7.8% each, and GH insensitivity syndrome in 4.1%

cases. In a study to evaluate prevalence and etiological profile of short stature in children attending out patient department (OPD) of a community-level hospital, the prevalence of short stature was 13.8%; significantly higher than prevalence reported from tertiary centers. The most common cause of short stature was PEM and chronic diseases occurring in 53.5% cases. Other causes included normal variant short stature 24.4%, endocrine problems 4.7% and miscellaneous 5.8%. 11.6% could not be classified due to loss to follow-up and inability to refer to tertiary centers.

CAUSES OF SHORT STATURE

Proportionate Short Stature

Normal Variants (*Table 1*)

- Familial
- Constitutional delay in growth and puberty.

Prenatal Causes

- Intrauterine growth restriction (placental, infections or teratogen)
- Genetic disorders (chromosomal and metabolic disorders).

Postnatal Causes

- Under nutrition
- Chronic systemic illness
- Psychosocial short stature (emotional deprivation)
- Endocrine causes
 - Growth hormone deficiency/insensitivity
 - Hypothyroidism
 - Juvenile diabetes mellitus
 - Cushing's syndrome
 - Pseudohypoparathyroidism
 - Precocious/delayed puberty.

Disproportionate Short Stature

With Short Limbs

- Achondroplasia, hypochondroplasia, chondrodysplasia punctata, chondroectodermal dysplasia, diastrophic dysplasia, metaphyseal chondrodysplasia
- Deformities due to osteogenesis imperfecta, refractory rickets.

With Short Trunk

- Spondyloepiphyseal dysplasia, mucopolidosis, mucopolysaccharidosis
- Caries spine, hemivertebrae.

TABLE 1 | Comparison between familial short stature and constitutional short stature

Features	Familial short stature	Constitutional delay in growth
Sex	Both equally affected	More common in boys
Length at birth	Normal	Normal (starts falling < 5th centile in 1st 3 years of life)
Family history	Short stature	Delayed puberty
Parents stature	Short (one or both)	Average
Height velocity	Normal	Normal
Puberty	Normal	Delayed
Bone age (BA) and chronological age (CA)	BA = CA > height age	CA > BA = height age
Final height	Short, but normal for target height	Normal

PRENATAL CAUSES

Intrauterine Growth Restriction

Arrest of fetal growth in early embryonic life causes reduction in total number of cells, leading to diminished growth potential in postnatal life. Although the majority of small for gestational age (SGA) infants show catch-up growth, about 20% may follow a lifelong pattern of short stature. In comparison, appropriate-for-gestational-age premature infants usually catch up to the normal range of height and weight by 1–2 years of age. Bone age, age at onset of puberty, and yearly growth rate are normal in SGA patients, and the patients are characteristically thin.³

Genetic Syndromes

Although classic Turner's syndrome of 45, XO (gonadal dysgenesis) is often correctly diagnosed, it is not always appreciated that any phenotypic female with short stature may have a variant of Turner's syndrome. Thus, a karyotype determination should be performed for every short girl if no other cause for short stature is found, especially if puberty is delayed. Other syndromes, e.g. Down syndrome, Noonan syndrome, Prader-Willi syndrome, Silver-Russell syndrome, Seckle syndrome, may be associated with short stature.

POSTNATAL CAUSES

Chronic Systemic Illness

Chronic illnesses that may lead to growth retardation are:

- Chronic infections
- Malabsorption syndromes
- *Birth defects*: Congenital heart defect (CHD), urinary tract and nervous system anomalies
- *Miscellaneous*: Cirrhosis of liver, bronchiectasis, acquired heart diseases, cardiomyopathies.

Endocrine Causes

Growth Hormone Deficiency

Classic GH deficiency, either alone or in conjunction with other pituitary hormone deficiencies, might also have a characteristic profile. Male patients may have a small penis (micropallus) and if in the neonatal period, hypoglycemia. The neonate with a micropallus should be tested for hypopituitarism initially, whereas the older child should be evaluated if there is evidence of growth failure. Affected GH-deficient female patients do not have abnormalities of genital development; however, because hypoglycemia is often a component of hypopituitarism, it is still a clue. Children with classic GH deficiency are often said to have a pudgy, cherubic appearance, in part because height is usually more affected than weight and the

deficiency is associated with a characteristic distribution of fat in the face and abdomen.

Laron's Syndrome

Conditions of GH insensitivity, also referred to as primary IGF-1 deficiency, encompass a variety of genetic conditions characterized by growth failure, high serum GH levels, and very low serum IGF-1 levels.⁴ The phenotypic characteristics of GH insensitivity include growth failure evident at birth⁵ with postnatal subnormal growth velocities and stature -4 to -10 SD below the mean.⁴ Patients also have a subnormal head circumference, protruding forehead, abnormal upper- to lower-body ratio, short extremities, and sparse hair. The genitalia are small, and puberty is delayed, but fertility is normal. Metabolically, the most striking feature of IGF-1 deficiency is hypoglycemia with later development of obesity, relative hyperinsulinemia, and insulin resistance.⁶

Type-1 Diabetes Mellitus

Although weight loss may occur immediately before the onset of clinically apparent insulin-dependent diabetes mellitus (IDDM), children with new-onset diabetes are frequently taller than their peer group, possibly because GH and insulin levels are increased during the preclinical evolution of the disease.^{7–9} Most children with IDDM, even those with marginal control,¹⁰ grow quite normally, especially in prepubertal years, although growth velocity may decrease during puberty.¹¹ However, growth failure can occur in diabetic children with long-standing poor glycemic control.^{12,13}

Hypothyroidism

Untreated severe congenital hypothyroidism results in profound growth failure. With proper treatment, however, children with congenital hypothyroidism reach a height appropriate for their genetic potential.¹⁴ Acquired hypothyroidism during childhood may also result in growth failure that can range from subtle to profound, depending on the severity and duration of the hypothyroidism. Growth failure may be the most prominent manifestation of hypothyroidism in children.¹⁵ The poor growth is more apparent in height than in weight gain, so these children tend to be overweight for height. Skeletal maturation is delayed in those children in whom the hypothyroidism was sufficient to retard growth, with the BA at diagnosis corresponding to the age at onset of the hypothyroidism.¹⁵ Body proportion is immature, with an increased upper-to-lower body segment ratio.

In those children with severe growth failure, treatment with thyroid hormone results in rapid catch-up growth. This is typically accompanied by marked skeletal maturation. In cases of prolonged severe hypothyroidism, the advancement of skeletal maturation

with treatment can exceed the growth acceleration, resulting in a compromised adult height.¹⁵ The deficit in adult stature correlates with the duration of hypothyroidism before initiation of treatment. Catch-up growth may be particularly compromised if therapy is initiated near puberty.¹⁶

Cushing's Syndrome

Glucocorticoid excess impairs skeletal growth, interferes with normal bone metabolism by inhibiting osteoblastic activity, and enhances bone resorption.¹⁷⁻¹⁹ These effects are related to the duration of steroid excess,²⁰ regardless of whether the Cushing's syndrome is due to adrenocorticotrophic hormone (ACTH) hypersecretion, adrenal tumor, or glucocorticoid administration. The longer the duration and the greater the intensity of glucocorticoid excess, the less likely is catch-up growth to be completed. Alternate-day glucocorticoid treatment decreases but does not eliminate the risk of growth suppression.²¹⁻²³ Inhaled glucocorticoids given for the treatment of asthma have an even lower risk of growth suppression.²⁴⁻²⁶

Rickets

In the past, hypovitaminosis D was a major cause of short stature and was often associated with other causes of growth failure, such as malnutrition, prematurity, malabsorption, hepatic disease, or chronic renal failure (CRF). In isolated vitamin D deficiency, breast-fed infants typically have poor exposure to sunlight and are not nutritionally supplemented with vitamin D. Characteristic skeletal manifestations of rickets include frontal bossing, craniotables, rachitic rosary, and bowing of the legs. Such children usually begin to synthesize 1, 25-dihydroxyvitamin D₃ as they become older, broaden their diet, and have increased exposure to sunlight, with amelioration of the transient early decrease of linear growth velocity.

Psychosocial Short Stature

An extreme form of failure to thrive is termed psychosocial dwarfism or emotional deprivation dwarfism.²⁷⁻²⁹ Most cases of failure to thrive can be traced back to a poor home environment and inadequate parenting, with improved weight gain and growth upon removal of the infant from the dysfunctional home. Some children have been reported, however, to show dramatic behavioral manifestations beyond those in the typical failure-to-thrive infant, namely bizarre eating and drinking habits, such as drinking from toilets, social withdrawal, and primitive speech.²⁸ Hyperphagia and abnormalities of GH production may be associated.³⁰ The reversibility of GH secretory defects and the later growth increment in the context of the clinical findings described previously confirm the diagnosis of psychosocial dwarfism.³¹⁻³⁴

SKELETAL DYSPLASIAS

The osteochondrodysplasias encompass a heterogeneous group of disorders characterized by intrinsic abnormalities of cartilage and bone.^{35,36} These disorders include abnormalities in the size or shape of bones in the limbs, spine, or skull, often with abnormalities seen on radiographic evaluation. Diagnosis of osteochondrodysplasias can be difficult, with clinical and radiologic evaluation central to the diagnosis. The family history is critical, although many cases are caused by *de novo* mutations, and this is generally the case in autosomal-dominant achondrodysplasia and hypochondrodysplasia. Measurement of body proportions should include arm span, sitting height, upper and lower body segments, and head circumference.

ASSESSMENT OF A CHILD WITH SHORT STATURE

A detailed history and physical examination (**Tables 2 and 3**) are the cornerstones for the etiological diagnosis of short stature. The key issues which help in deciding the cause are:

Accurate Height Measurement

- Below 2 years: Supine length with infantometer
- For older children: Stadiometer.

Assessment of Body Proportion

- Upper segment: Lower segment ratio
 - Increased ratio: Rickets, achondroplasia, untreated hypothyroidism
 - Decreased ratio: Spondyloepiphysealdysplasia, vertebral anomalies
 - Comparison of arm span with height.

Assessment of Height Velocity

The rate of increase in height over a period of time, expressed as cm/year. If low, it suggests pathological cause of short stature.

Comparison with Population Norms

Height plotted on appropriate growth charts (**Figure 1**) and expressed as centile or SD score.

TABLE 2 | Clues to etiology of short stature from history

History	Etiology
History of delay of puberty in parents	Constitutional delay of growth
Low birth weight	SGA
Neonatal hypoglycemia, jaundice, micropenis	GH deficiency
Dietary intake	Undernutrition
Headache, vomiting, visual problem	Pituitary/hypothalamic SOL
Lethargy, constipation, weight gain	Hypothyroidism
Polyuria	CRF, RTA
Social history	Psychosocial dwarfism
Diarrhea, greasy stools	Malabsorption

Abbreviations: GH, Growth hormone; SGA, Small for gestational age; SOL, Space-occupying lesion; CRF, Chronic renal failure; RTA, Renal tubular acidosis

TABLE 3 | Clues to etiology short stature from examination

Examination findings	Etiology
Disproportion	Skeletal dysplasia, rickets, hypothyroidism
Dysmorphism	Congenital syndromes
Hypertension	Chronic renal failure
Goiter, coarse skin	Hypothyroidism
Central obesity, striae	Cushing's syndrome

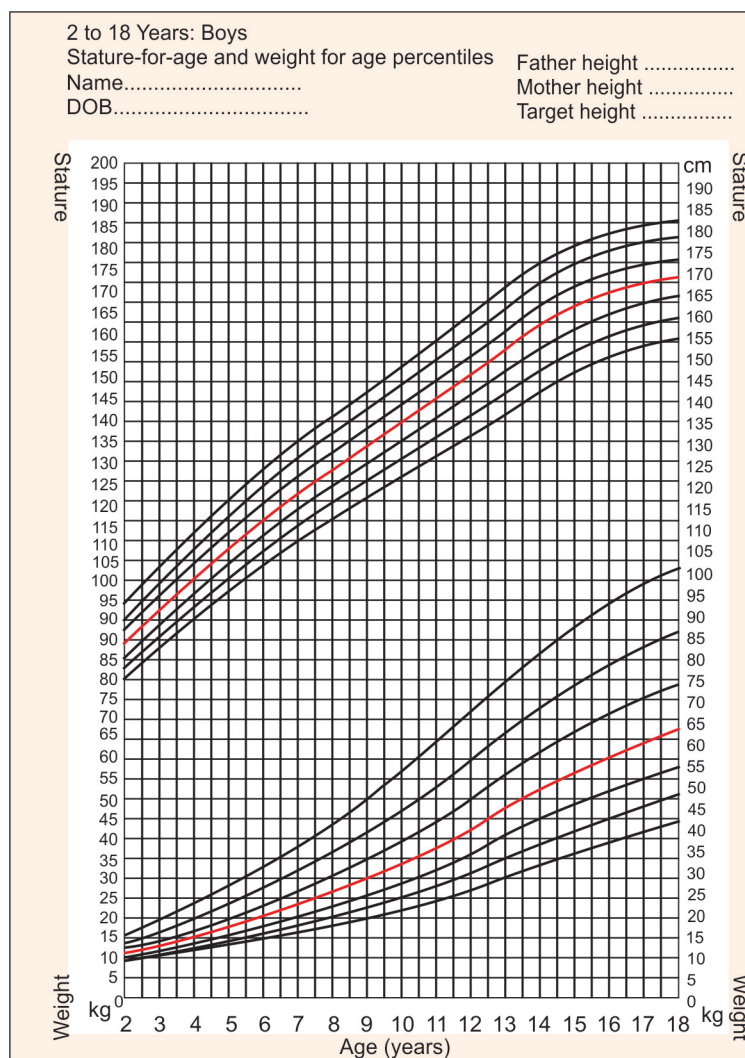


Figure 1: Growth chart
Courtesy: Indian Academy of Pediatrics

Comparison with Child's Own Genetic Potential

- Mid-parental height for boys = $(\text{Mother's height} + \text{father's height})/2 + 6.5 \text{ cm} \pm 8 \text{ cm}$
- Mid-parental height for girls = $(\text{Mother's height} + \text{father's height})/2 - 6.5 \text{ cm} \pm 8 \text{ cm}$.

The target height is plotted on the growth chart and if the child is falling within the target height, the cause could be genetic or constitutional. Otherwise, it is considered abnormal.

Sexual Maturity Rating

- Also known as Tanner's stages (**Figure 2**)
- Used in older children
- Total five stages included in each gender.

Bone Age

Bone age assessment should be done in all children with short stature.

- Appearance of various epiphyseal centers and fusion of epiphyses with metaphyses tells about the skeletal maturity of the child.
- Conventionally read from X-ray of hand and wrist using Gruelich-Pyle atlas or Tanner-Whitehouse method.

- Bone age gives an idea as to what proportion of adult height has been achieved by the child and what is remaining potential for height gain.
- Bone age is delayed compared to CA in almost all causes of pathological short stature.

INVESTIGATIONS

Level 1 (Essential Investigations)

- Complete hemogram with erythrocyte sedimentation rate (ESR)
- Bone age
- Urinalysis (microscopy, pH, osmolality)
- Stool (parasites, steatorrhea, occult blood)
- Blood (renal function test, calcium, phosphate, alkaline phosphatase, venous gas, fasting sugar, albumin, transaminases).

Level 2

- Serum thyroxine, thyroid-stimulating hormone (TSH)
 - Karyotype to rule out Turner's syndrome in girls
- If above investigations are normal and height between -2 to -3 SD, then observe height velocity for 6–12 months.
If height < 3 SD, proceed to level 3 investigations.

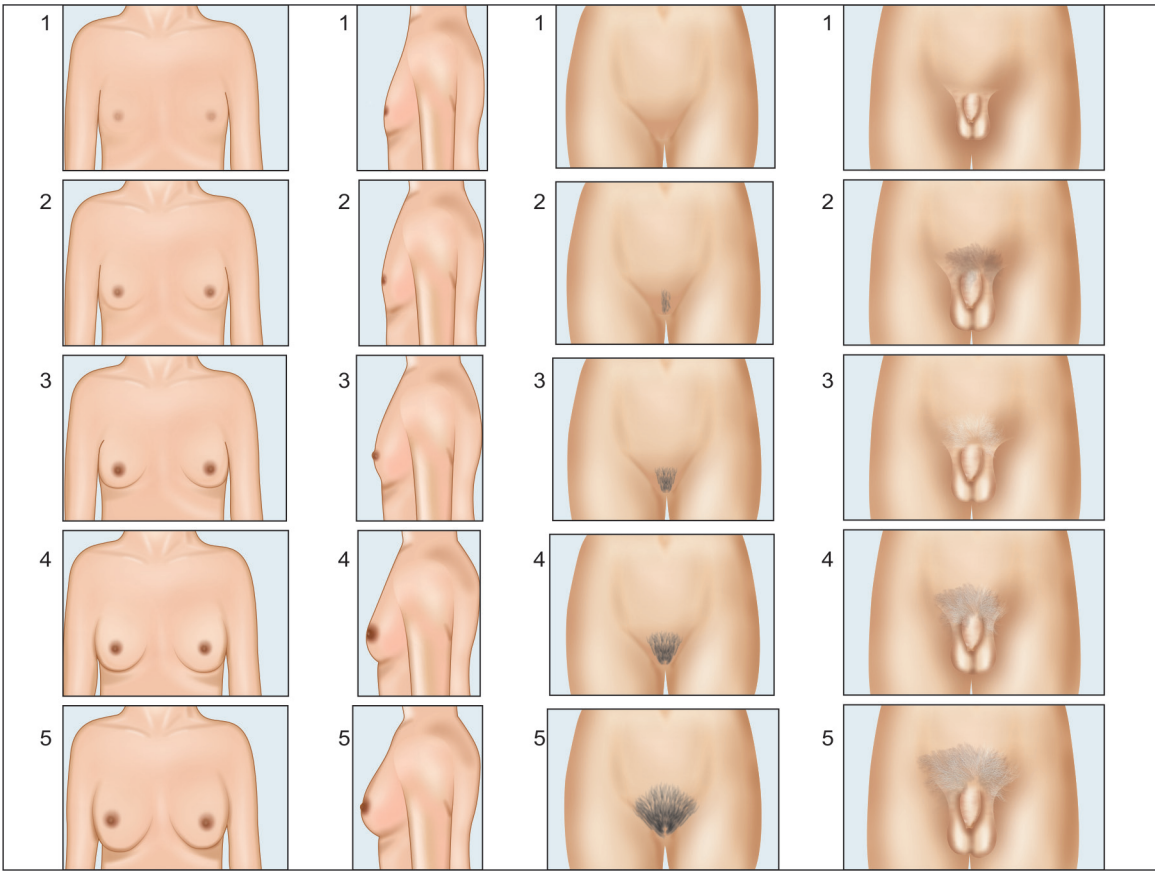


Figure 2: Tanner's stages

Level 3

- Celiac serology (anti-endomysial or anti-tissue transglutaminase antibodies)
- Duodenal biopsy
- Growth hormone stimulation test with glucagon or insulin and serum IGF-1 levels.

MANAGEMENT

- Counseling of parents (for physiological causes)
- Dietary advice [undernutrition, celiac disease, renal tubular acidosis (RTA)]
- Limb lengthening procedure: Skeletal dysplasia
- Levothyroxine (in hypothyroidism)
- Growth hormone subcutaneous injections (GH deficiency, Turner syndrome, SGA, CRF prior to transplant)
- Monitoring with regular and accurate recording of height is mandatory for a good outcome in any form of therapy.

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