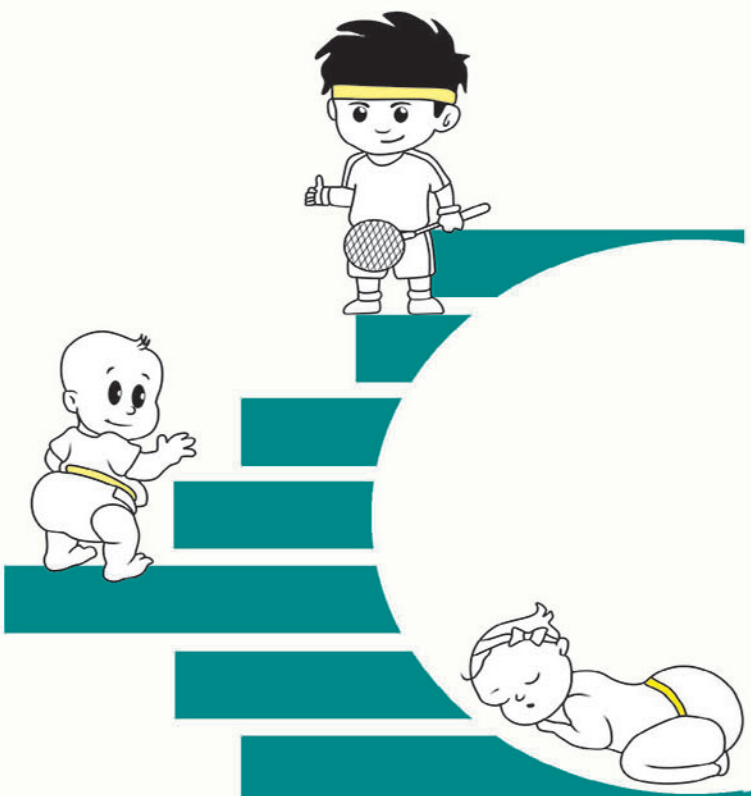
INDIAN ACADEMY OF PEDIATRICS
GROWTH, DEVELOPMENT AND BEHAVIORAL PEDIATRICS CHAPTER

Textbook of Growth, Development & Behavioral PEDIATRICS



Chief Editors
Anjana Thadhani
Ashok Rai

Academic Editor
Jaydeep Choudhury

Associate Editors
Suchit Tamboli
Suneel Godbole
Amola Patel

JAYPEE

Contents

SECTION 1: Growth in Children

SECTION 2: Child Development

SECTION 3: Behavior

SECTION 4: Early Intervention Section

SECTION 5: Growth Charts and Developmental Assessment Tests

CHAPTER 3

Approach to Abnormalities of Linear Growth

Anurag Bajpai, Riddhi Patel

INTRODUCTION

The appropriate evaluation of growth disorders involves accurate measurement of anthropometric parameters, plotting on population-specific growth charts, and its correct interpretation. The aim is to avoid unnecessary workup in physiological cases while not missing the pathology.

PATHOPHYSIOLOGY

There are four phases of growth throughout the lifespan of humans—(1) the rapid growth phase of the fetal, (2) infantile, (3) slow growth childhood, and (4) pubertal period **(Fig. 1)**.

The fetal phase is characterized by maximum linear growth of 50 cm in the first two trimesters, and weight gain happens during the third trimester. This phase is mainly regulated by nutrient supply via the placenta with the limited role of growth hormone (GH) and thyroxine. So, fetuses with complete GH deficiency and hypothyroidism have normal length at birth. The placental damage in early pregnancy leads to symmetrical growth retardation, while later problems are associated with asymmetrical (only weight is affected) growth restriction. The fetus with growth failure due to adverse maternal and placental factors usually catch up more than those with intrinsic factors. Excess nutrient delivery via the placenta, as in gestational diabetes, is associated with large for gestational-age newborns.

Infantile growth is also primarily driven by nutrition, with a 30–35 cm gain in linear growth. The characteristic feature of this phase is a shift from environmentally influenced birth size toward genetic potential determined

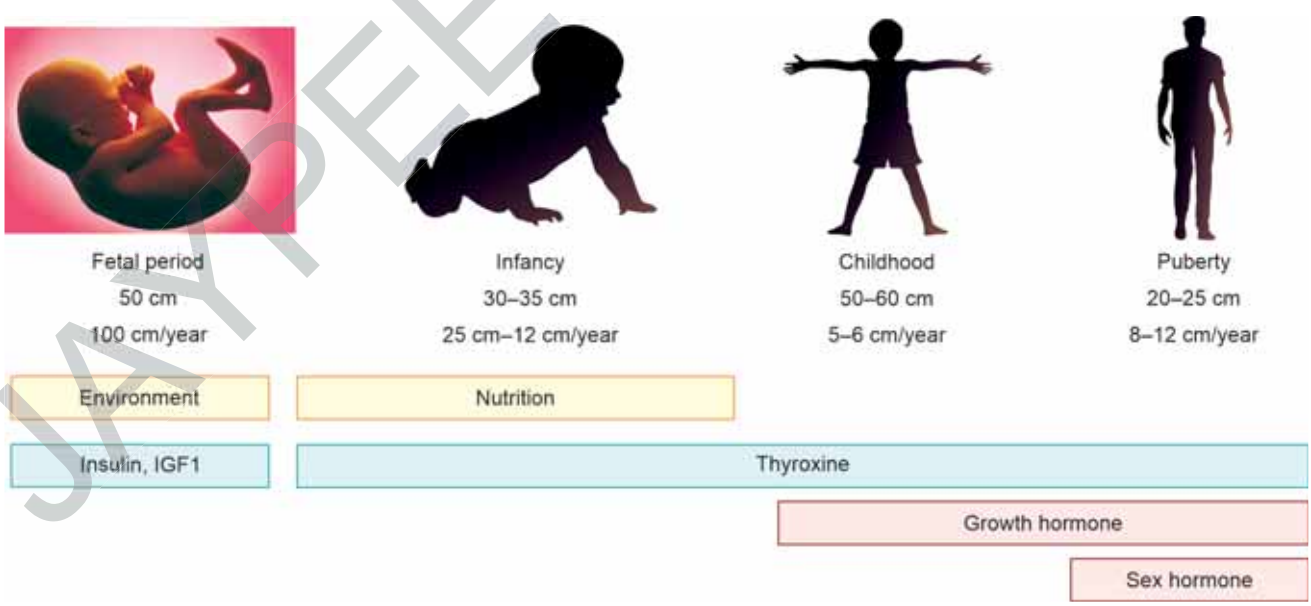


Fig. 1: Phases of growth and their regulation. (IGF-1: insulin-like growth factor 1)

Source: Adapted with permission from Bajpai A, Agarwal N. Growth failure. In: Bajpai A, Patel R, Dave C, Agarwal N (Eds). MedEClasses Pediatric Endocrinology. Kanpur: Grow Society Publication; 2019; pp. 49-53.

by parental stature. Therefore, crossing percentile lines according to the genetic potential during this phase is not a cause of concern.

Childhood growth occurs at a rate of 4–6 cm/year. It is mainly regulated by growth GH-insulin-like growth factor 1 (IGF1) axis and thyroid hormones. GH is released in a pulsatile fashion due to the reciprocal interaction of GH-releasing hormone (GHRH) and somatostatin. Growth promoting effect of GH requires adequate nutrition, normal thyroid function, and a normal skeleton. Crossing percentile lines between 2 years and puberty is significant. Growth during the prepubertal childhood phase significantly contributes to final adult height.

Pubertal growth accounts for 20–25% of adult height. During this phase, the pulsatility of GH increases under the influence of gonadal steroids. Pubertal growth spurt begins at breast stage II in girls and a testicular volume of 10 mL in boys. Estrogen in both girls and boys matures epiphyseal growth and eventually causes epiphyseal fusion and cessation of growth. Postpubertal growth is only 5–8 cm in both genders. The average adult height is 13 cm higher in men than women due to the later onset of puberty and higher pubertal growth velocity.

REGULATION OF GROWTH

Final adult height is determined 60–80% by genetics, 20–30% by nutrition, and 10–15% by endocrine factors. Type I nutrients (vitamins, calcium, magnesium, and iodine) and type 2 nutrients (proteins, electrolytes, zinc, and phosphorus) play a vital role in growth regulation. Endocrine regulations of growth are GH, thyroxine, and sex steroids. GHRH from the hypothalamus acts on the pituitary to produce GH (*see* **Fig. 1**). GH is released in a pulsatile fashion due to the reciprocal interaction of GHRH and somatostatin. Therefore, basal GH has a limited role in diagnosing GH deficiency. GH acts on the GH receptor in the liver to produce IGF1. Growth promoting effect of GH requires adequate nutrition, normal thyroid function, and a normal skeleton. Thyroid hormones are essential for postnatal growth and skeletal maturation. The patients with hypothyroidism have blunted GH hormone secretion and poor response to GH provocative test; hypothyroidism must be ruled out before advising GH stimulation tests. Estrogen induces GH secretion during puberty in both sexes, indicating the need for priming with estrogen in prepubertal boys >11 years and girls >10 years before performing dynamic GH tests. Dynamic tests for GH deficiency include stimulation of GH secretion by various provocative agents and for GH excess suppression by glucose.

ANTHROPOMETRY

Accurate growth assessment involves correctly measuring anthropometric parameters with calibrated and maintained equipment.

Linear growth measurement is essential for monitoring growth in infants and children. Supine length is measured in children below 2 years of age and children with neuromuscular disorders using an infantometer. A wall-mounted stadiometer does standing height in older children and adolescents. *Weight* is an important parameter of nutritional status. It is measured preferably on an electronic weighing scale with zero error. Assessment of *body proportion* gives an important diagnostic clue to skeletal dysplasia. The upper segment/lower segment ratio is calculated by measuring the sitting height or lower segment. Arm span is equal to height; its abnormal relationship with height is seen in some skeletal dysplasia and connective tissue disorders such as Marfan syndrome or homocystinuria. Growth velocity should be measured over at least 6 months–1 year to identify the disease.

GROWTH CHARTS

The ideal growth chart is updated in the last 10 years, population-representative, and designed to overcome confounders like nutrition. The current recommendation by the Indian Academy of Pediatrics (IAP) is to use the World Health Organization (WHO) 2006 growth standard for children aged 0–5 years and revised IAP 2015 growth reference from 5 to 18 years. IAP 2015 charts are superior to the WHO and IAP 2007 charts in identifying pathological short stature. For monitoring growth in preterm babies, intergrowth 21 charts are used till the corrected gestational age of 1 year.

PUBERTAL DEVELOPMENT

The development of secondary sexual characteristics, changes in gonadal and reproductive organs, skeletal maturation, and changes in body composition characterizes puberty. Pubertal development in girls begins with breast budding at an average age of 10.2 years, followed by pubic and axillary hair development **(Fig. 2)**. It is also associated with increased ovarian volume, uterine size, and cervical length. Clear, watery vaginal discharge indicates imminent menarche. The first sign of pubertal

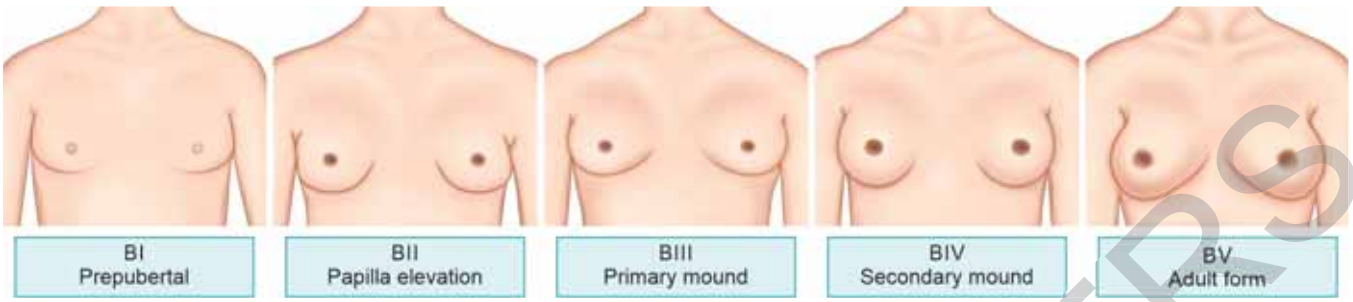


Fig. 2: Stages of pubertal development in girls.
Source: Adapted with permission from Agarwal N, Bajpai A. Growth physiology. In: Bajpai A, Dave C, Agarwal N, Patel R (Eds). MedEClasses Textbook of Pediatric Endocrinology: Basic Pediatric Endocrinology, 1st edition. MedEClasses; 2019. pp. 55-64.

Fig. 3: Stages of pubertal development in boys.
Source: Adapted with permission from Agarwal N, Bajpai A. Growth physiology. In: Bajpai A, Dave C, Agarwal N, Patel R (Eds). MedEClasses Textbook of Pediatric Endocrinology: Basic Pediatric Endocrinology, 1st edition. MedEClasses; 2019. pp. 55-64.

development in boys is an increase in testicular volume above 4 mL, followed by an increase in penile length and width. Other changes include changes in voice, pubic, axillary, facial hair growth, and spermatogenesis **(Fig. 3)**.

SHORT STATURE

Short stature represents the most common clinical presentation to pediatricians. While most children with short stature have a physiological cause, a significant proportion has a pathological cause.

Criteria: Evaluation of short stature is required in short children (height below the third percentile or 2 SD (standard deviations) below mean for age and gender and 1.5 SD below mid-parental height), growing slowly (less than the 25th percentile), or not growing at all (crossing of two or more percentile lines between 2 years and puberty).

Etiology

As described above, interruptions in any factors regulating linear growth may cause short stature. The etiology of short stature can be physiological (familial short stature, constitutional delay in growth and puberty) or pathological (primarily due to intrinsic defect in the growth plate or secondary due to changes in the environment of the growth plate) **(Flowchart 1)**.

Physiological short stature: These accounts for most cases of short stature. Their identification avoids unnecessary workup. Differentiating features of constitutional delay of growth and puberty (CDGP) and familial short stature (FSS) are described in **Table 1**.

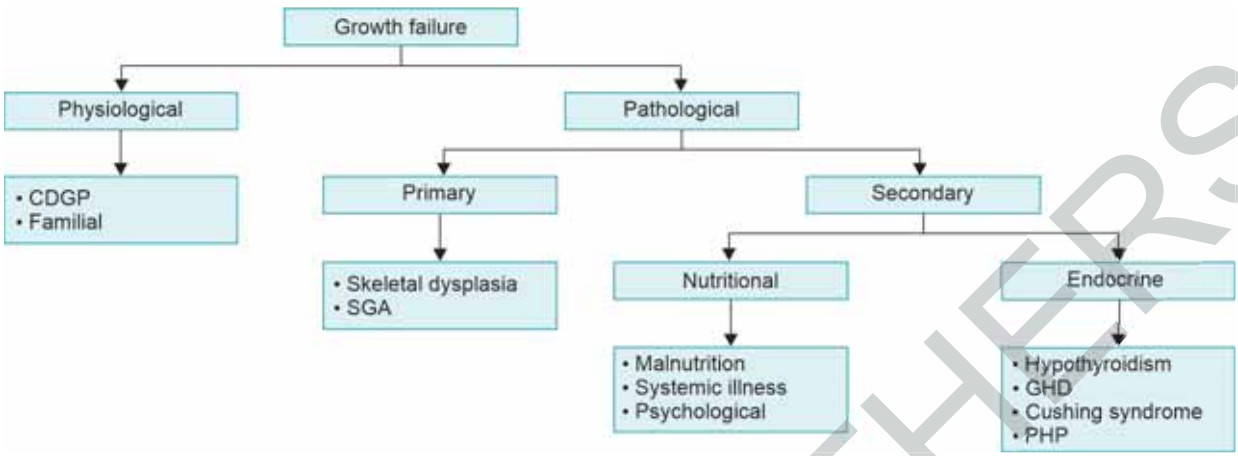
Pathological short stature: These include intrinsic abnormality of the growth plate and nutritional and endocrine causes of short stature.

Primary Disorder

These include abnormality of growth plate cartilage, microarchitecture, and bone.

Skeletal dysplasia involves multiple conditions associated with disproportionate short stature and other abnormalities, of which fibroblast growth factor receptor 3

Flowchart 1: Etiology of growth failure.



(CDGP: constitutional delay of growth and puberty; GHD: growth hormone deficiency; PHP: pseudohypoparathyroidism; SGA: small for gestational age)

TABLE 1: Difference between CDGP and familial short stature.

Characteristics	*CDGP*	*Familial short stature*
Bone age	Delay	Normal
Growth velocity	Normal	Normal
Family history of delayed pubertal onset	Present	Absent
Family history of short stature	Absent	Present
Final adult height	Normal	Compromised

(CDGP: constitutional delay of growth and puberty)

(FGFR3) defects present as achondroplasia and hypochondroplasia are most common. Most skeletal dysplasias are associated with short limbs except spondyloepiphyseal dysplasia, characterized by a short trunk.

Small for gestational age (SGA) is defined as birth length and/or weight <2 SD for gestational age. SGA is caused by maternal factors (malnutrition, infection), placental factors (insufficiency, abruption), or fetal factors (syndromes, malformations). About 70–80% of SGA catch up in the first 2–4 years of age. Those who fail to catch up may benefit from GH therapy. The GH should be started after excluding all other causes without GH provocative testing.

Genetic syndromes are characterized by severe short stature, dysmorphic facial features, delayed development, and other diagnostic pointers. Russell–Silver, Seckel, and Fanconi syndromes are associated with SGA.

Turner syndrome is the partial/complete absence of an X chromosome in a phenotypic female. Short stature is the most common feature of this condition. Other features include webbing of the neck, low posterior hairline, shield chest, cubitus valgus, brachymetacarpia, left-sided obstructive lesion of the heart, lymphedema, and delayed puberty. Puberty may be normal, and all other typical features may be absent in mosaic turner syndrome. A karyotype with 50 metaphases is ordered in all girls with normal screening tests and unexplained short stature.

Secondary Disorder

These include the abnormality of factors regulating growth plate homeostasis.

Chronic systemic illness can cause growth failure due to various factors such as chronic anemia, malnutrition, tissue hypoxia, metabolic acidosis, side effects of treatment (glucocorticoids), and modified GH secretion and action. Major disorders include gastrointestinal (celiac disease, inflammatory bowel disease), respiratory (chronic asthma, cystic fibrosis), cardiac (congenital heart disease), renal (renal tubular acidosis, chronic kidney disease), chronic liver disease, hematological (hemolytic anemia), chronic infection (tuberculosis). Many of these disorders present as isolated short stature, so comprehensive assessment of all systemic illnesses is mandatory in any straightforward child. These disorders are characterized by delayed bone age and delayed puberty, with a more significant effect on weight than height.

Malnutrition is one of the important causes of short stature in India. Type II nutrient (zinc, iron, and proteins) deficiency is associated with poor growth. It is GH resistant state characterized by high GH and low IGF1. Anorexia

nervosa is an extreme form of malnutrition in adolescents associated with growth failure.

Endocrine causes of short stature include hypothyroidism, growth hormone deficiency (GHD), pseudohypoparathyroidism, and Cushing syndrome.

Hypothyroidism: Thyroxine plays a vital role in normal growth throughout infancy, childhood, and adolescents. Untreated congenital or acquired hypothyroidism can cause severe growth retardation. Hypothyroidism can affect the entire growth hormone-insulin-like growth factor 1 (GH-IGF1) axis and direct growth plate. Many times, classic symptoms of hypothyroidism are not evident. Therefore, thyroid function needs to be evaluated in any child presenting with short stature. Also, hypothyroidism blunts GH secretion, GH stimulation test is always performed after establishing euthyroid status. Thyroxine therapy accelerates skeletal maturation causing rapid catch-up and compromising final height.

Growth hormone deficiency may be isolated or part of multiple pituitary hormone deficiency (MPHD). GHD may present in neonatal life when associated with hypopituitarism, but isolated GHD is diagnosed at an average age of 6–8 years. MPHD occurs due to CNS insult, CNS tumor, congenital malformation of the brain, or various genetic defects (LHX3, LHX4, SOX2, HESX1, POU1F1, and PROP1). Isolated GHD is most commonly idiopathic or may occur secondary to CNS pathology or genetic cause. GHD presents normal birth weight and length except for some genetic forms (*IGF1* gene mutation presents with intrauterine growth retardation). The onset of short stature begins after infancy and is associated with severe short stature. Typical phenotypic features of GHD are the cherubic face, midfacial hypoplasia, delayed dentition, central obesity, micropenis, and undescended testis. GH insensitivity due to GH receptor defect, *IGF1* gene deletion, and IGF1 receptor defect is associated with more severe short stature, sparse hair, coarse face, shallow orbit, and hypoplastic nasal bridge. Acquired GHD presents with faltering growth and weight gain associated with other features such as nystagmus, squint, polyuria, polydipsia (posterior pituitary damage), and hyperphagia.

Cushing syndrome: Excess glucocorticoids (exogenous or endogenous) impair growth by suppressing the GH-IGF1 axis and direct action on the growth plate. The most common cause of Cushing syndrome is pharmacological doses of steroids for various chronic disorders. The most common presentation of Cushing syndrome is short stature with weight gain. Unsuppressed morning cortisol level after overnight dexamethasone suppression test suggests the possibility of endogenous cortisol excess.

Pseudohypoparathyroidism: The condition is associated with end-organ resistance to parathyroid hormone (PTH) and presents with the typical phenotype of round face, obesity, mental retardation, brachymetacarpia, tetany, and intracranial calcification. Characteristic biochemical findings of low calcium and elevated phosphorus with normal or increased PTH establish the diagnosis.

Assessment

Assessment of a short child involves confirmation of short stature, identification of physiological variant by appropriate history, pubertal examination and interpretation of growth charts, identification of specific pointers to diagnosis on history and physical examination, differentiation of nutritional and endocrine cause of short stature and confirmation of diagnosis by targeted investigations.

Confirmation of Short Stature

The first question to answer before evaluation is whether the child is short. Appropriately measured supine length/standing height and mid-parental height are plotted on population-specific growth charts. The deviation of growth from normal is expressed as a percentile (rank) or standard deviation score (SDS, number of standard deviations beyond mean). The likelihood of pathology increases with the severity of growth failure. It is very low (below 2%) with a height SDS above –2 (around the third percentile) and increases to around 50% between –2 and –3 and 80% beyond –3 SDS (0.1 percentile). Immediate evaluation is required in children with height SDS below –3. Children with a height SDS between –2 and –3 should be followed up for growth velocity over 6–12 months; growth velocity below the 25th percentile in the setting suggests the need for evaluation. Evaluation is not required with a height SDS above –2 without pointers to growth disorders. Individuals with acquired growth failure may present with reduced growth velocity and may need evaluation even if height SDS is above –2. Crossing two or more major percentile lines between the age of 2 years and puberty suggests the need for a workup. However, a decline in growth percentile in large-for-age neonates commensurate to family potential represents physiological catch-down growth and does not need evaluation.

Identification of Physiological Short Stature

Physiological and pathological causes of short stature are differentiated by careful family history, correct interpretation of growth charts, and pubertal assessment. The children growing at stable growth velocity and predicted adult height in the target height range are familial short stature. Estimating target height (adding 6.5 cm for boys and subtracting 6.5 cm for girls to the average parental height). A height SDS within 1.5 SDS of the target height SDS suggests short familial stature. The children with mildly delayed growth, bone age, and puberty and positive family history of delayed puberty and delayed catch-up suggest the diagnosis of CDGP. The height is low for the age but normal for the level of skeletal maturation (height SDS for bone age above –2). Catch down to catch genetic potential in the first 2 years of life and physiological dip in prepubertal years do not need extensive workup.

Identification of Primary Growth Disorder

Careful assessment of body proportion, dysmorphic facial features, and associated abnormality provides the diagnostic clue to associated syndromes or skeletal dysplasia.

Differentiation of Nutritional and Endocrine Cause

After excluding physiological and primary growth disorders, the next step is to differentiate nutritional and endocrine causes. Detailed history regarding antenatal period, birth weight/length, associated complaints (gastrointestinal symptoms, pica, constipation, easy fatigability, and polyuria), symptoms of systemic illness (renal, hepatic, neurological, and respiratory disorder), developmental history, and detailed diet history should be taken. Nutritional causes of short stature are associated with a more significant impact on weight than height [body mass index (BMI) standard deviation score less than –1 or weight age lower than height age]. At the same time, endocrine etiology is suspected in the short and plump child. Pointers to the etiology of growth failure should be assessed.

Investigations

Provision diagnosis is made on initial history, and biochemical and radiological investigations confirm physical examination. Children with no suspicion of underlying cause on primary assessment should undergo screening evaluation.

Bone age assessment: X-ray left hand and wrist is used for bone age assessment. It also gives an idea of metabolic bone disease, skeletal abnormality (brachymetacarpia), and dysplastic bone (metaphyseal or epiphyseal irregularity). Bone age can be determined by the maturation of the epiphyseal center by visual comparison (Greulich-Pyle, Gilsanz-Ratib), scoring the area of interest (Tanner–Whitehouse method), or automated methods (Bone Expert). Carpal bones are preferred in infancy (up to 10 months in girls and 14 months in boys), followed by phalangeal epiphysis (till 2 years in girls and 3 years in boys). A comparison of the size of epiphysis to metaphysis is indicated in prepuberty to early/mid-puberty. Epiphyses are smaller than metaphysis till 7 years of age in girls and 9 years in boys. They become equal to metaphysis by 10–12 years, bigger beyond 12 years with capping and fusion by 14 years of age. Fusion of distal epiphysis is assessed during late puberty (13–15 years in girls and 14–16 years in boys with a focus on long bones subsequently). Compared to chronological age, the degree of bone age delay gives a clue to the underlying cause.

Biochemical Evaluation

Laboratory screening investigations include complete blood count (CBC), electrolytes (sodium, potassium, metabolic bone profile (calcium, phosphorus, alkaline phosphatase), liver function (SGPT), renal function (creatinine), erythrocyte sedimentation rate, thyroid function test (free T4, TSH), blood sugar, anti-tissue transglutaminase antibody IgA (TTG), blood gas in children younger than 3 years. Every short girl with normal screening results for Turner syndrome should be ruled out by karyotype with 50 metaphases. In children with normal screening tests and unexplained short stature, further testing includes evaluation of the GH-IGF1 axis, genetic tests (syndromes, GH resistance), and neuroimaging of the hypothalamopituitary region (congenital malformation, tumor).

Assessment of Growth Hormone-Insulin-like Growth Factor 1 Axis

Growth hormone-insulin-like growth factor 1 axis evaluation should be done only after excluding all other causes of growth failure and when there is a high pretest probability, as most of these tests are inaccurate. Basal

GH is not used for diagnosing GHD due to the pulsatile secretion of GH. Various provocative agents (clonidine, arginine, insulin, glucagon, and GHRH) stimulate GH secretion. Peak stimulated GH level <5 ng/mL indicates complete GHD, a level between 5 and 10 ng/mL suggests partial GH insufficiency, and a level >10 ng/mL rules out GHD. Sex steroid priming is a must in prepubertal girls >10 years and boys >11 years who have predicted adult height in the target height range to avoid false positive results. Diagnosis of GHD is made with low IGF1 level without GH stimulation test in children with MPHD, abnormal neuroimaging (hypoplastic anterior pituitary, ectopic posterior pituitary, and absent stalk), or neurological insult (trauma, tumor, radiation, and neurosurgery). Low IGF1 levels with normal GH stimulation test suggest the possibility of GH insensitivity needs confirmation by genetic testing.

Approach

The evaluation is guided by the severity of growth failure (height SDS or percentile), familial component (corrected height SDS), skeletal maturation (height SDS for bone age), and nutritional effect (weight age and BMI SDS). No evaluation is needed with a height SDS above –2 (normal height), target height SDS above –1.5 (familial short stature), or height SDS for bone age above –2 (constitutional delay of puberty and growth). The first step of evaluation is screening tests and identifying primary growth disorder by appropriate clinical assessment (JPEM). The second step includes targeted investigation based on clinical markers. GH-IGF1 axis evaluation, neuroimaging, and genetic tests should be done only after excluding all the other causes **(Flowchart 2)**.

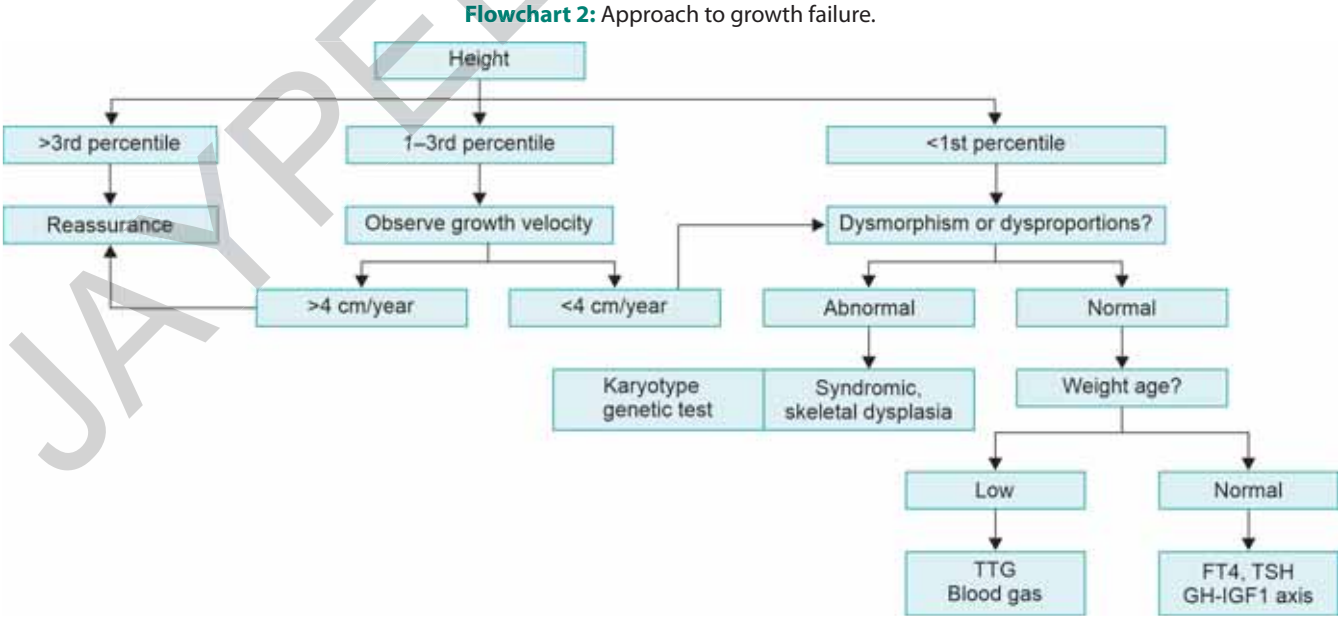
Management

After establishing the cause of short stature, treatment is directed to the cause. General measures include improving nutrition by protein, micronutrients, and calcium supplementation and advice regarding physical activity.

Physiological short stature: Observation and monitoring of growth velocity are the mainstays of therapy. FSS can be due to some inherited genetic cause (hypochondroplasia, SHOX mutation). If the height of one of the parents is too short (<2 SDS of the mean of the population), an evaluation of the underlying genetic condition should be done. A short course of sex steroids (testosterone 50 mg intramuscularly monthly for 3 months) induces puberty and growth spurt in children with CDGP.

Malnutrition and chronic illness: Improving nutritional status and treating underlying chronic illness result in catch-up growth. Specific measures include a gluten-free diet in celiac disease, alkali replacement in renal tubular acidosis, and thyroxine supplementation in hypothyroidism.

Flowchart 2: Approach to growth failure.



(FT4: free thyroxine; GH-IGF1: growth hormone-insulin-like growth factor 1; TTG: tissue transglutaminase; TSH: thyroid-stimulating hormone)

Growth hormone therapy: Besides GHD, GH therapy is approved for many other conditions **(Table 2)**. GH is a safe and effective therapy. Side effects of GH include headache, papilledema, glucose intolerance, fluid retention, and slipped capital femoral epiphysis.

TALL STATURE

Statistically, there are equal numbers of short and tall children but there are very few referrals of tall stature to pediatric outpatient due to acceptance by society as a normal phenomenon and very rarely initial presentation of underlying illness.

TABLE 2: FDA approved indication of GH therapy.

Indication	*Dose (µg/kg/day)*
GHD	25–50
Turner syndrome	50–60
SGA	35–70
Prader–Willi syndrome	25–35
Chronic renal failure	25–50
Idiopathic short stature	50–60
SHOX gene haploinsufficiency	50–60
Noonan syndrome	66

(FDA: Food and Drug Administration; GHD: growth hormone deficiency; SGA: small for gestational age)

Etiology

The tall stature can be physiological (constitutional), primary (sex chromosome abnormality, genetic syndromes due to connective tissue and metabolic abnormality, fetal overgrowth syndromes), and secondary (nutrition excess, hyperinsulinism, GH excess, hyperinsulinism, thyrotoxicosis, androgen/estrogen deficiency, estrogen resistance, ACTH resistance, and aromatase deficiency) **(Flowchart 3)**.

Constitutional tall stature is the most common cause of tall stature. Onset is in childhood, around 4 years. These children have normal puberty, their legs are relatively long, and their height is in the target range. They have higher GH secretion and GH sensitivity as compared to normal children.

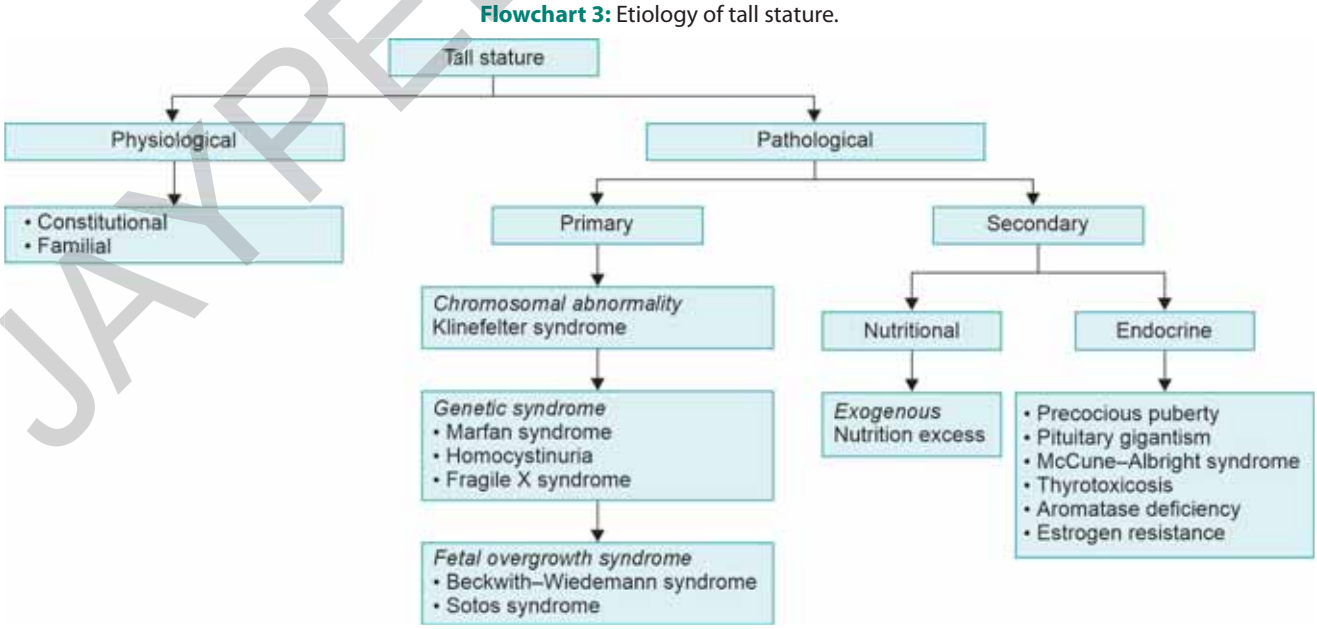
Exogenous obesity is a common cause of tall stature in childhood. Hyperinsulinism and advanced bone age due to high leptin levels cause tall stature. Their final adult height is within the target height range.

Syndromes

Some of the syndromes are associated with tall stature.

Marfan syndrome is caused by a fibrillin-1 (*FBN-1*) gene mutation. It is inherited in an autosomal dominant manner. Phenotypic features include hyperextensible joints, superior temporal subluxation of the lens, and aortic dissection/coarctation of the aorta with average intelligence.

Flowchart 3: Etiology of tall stature.



Klinefelter syndrome: The prevalence varies from 1:500 to 1:1,000. Most common sex chromosome aneuploidy presenting as tall stature. Increasing copies of the *SHOX* gene causes tall stature. They present in late adolescents with a lack of secondary sexual characteristics, learning difficulty, behavioral abnormality, mild mental retardation, or infertility. They have a eunuchoid appearance. Every tall boy with mental subnormality and decreased US/LS ratio should undergo karyotyping.

Homocystinuria is caused by cystathionine β-synthase gene mutation. It is inherited in an autosomal recessive manner. Phenotypically overlaps with Marfan syndrome except for inferior nasal subluxation of the lens, subnormal intelligence, and thromboembolic events in later life. The diagnosis is confirmed by increased serum homocysteine level.

Overgrowth Syndromes

Gestational diabetes is the most common cause of large for gestational age (LGA) infants. Even in the absence of clinical symptoms, evaluation for maternal diabetes is required in LGA babies. Other causes of fetal overgrowth are Sotos syndrome, Beckwith–Wiedemann syndrome (BWS), Marshall–Smith syndrome, Simpson–Golabi–Behmel syndrome, and Weaver syndrome. All the syndromes are associated with developmental delay.

Sotos syndrome (cerebral gigantism)—a mutation in the NSD1 gene causes this condition.

This child has birth length and weight above the 90th percentile, and this higher growth velocity persists till 4 years, then has normal growth and final adult height in the upper normal range. The characteristic features include a prominent forehead, dolichocephaly, hypertelorism, a pointed chin, large hands and feet, and cognitive delay.

Beckwith–Wiedemann syndrome is an imprinting disorder of genes (*IGF2, H19*) on chromosome 11p15.5. It is characterized by macrosomia and specific organ overgrowth. Clinical features include macroglossia, renomegaly due to renal medullary hyperplasia, neonatal refractory hypoglycemia due to islet cell hyperplasia, and developmental delay. Because of overgrowth, they have early puberty, early epiphyseal fusion, and normal adult height.

Endocrine Cause of Tall Stature

Both central and peripheral precocious puberty caused advanced skeletal maturation and accelerated growth velocity. Excess sex steroids advance growth plate rapidly and cause early epiphyseal fusion, eventually compromising final adult height. Sex hormone deficiency, as in the case of hypogonadotropic hypogonadism, causes delayed epiphyseal fusion, continued linear growth, and tall stature. Aromatase deficiency in males has tall stature due to a lack of epiphyseal fusion by estrogen. They also have learning difficulties and infertility.

Pituitary gigantism is very rare in children. It occurs secondary to GH-secreting pituitary adenoma or somatotroph hyperplasia. Tall stature is seen in adolescents before epiphyseal fusion. Other features are a large tongue, broad nose, enlarged hands and feet, and coarse facial features. IGF1 and IGHFBP3 are helpful screening tests. An oral glucose suppression test is the gold standard for the diagnosis. Neuroimaging is indicated in case of unsuppressed GH level to identify adenoma.

Isolated ACTH insensitivity: Familial glucocorticoid resistance caused by a mutation in ACTH receptor (MC2R) is associated with features of glucocorticoid deficiency (pigmentation, weakness, hyponatremia, and hypotension) and tall stature.

Thyrotoxicosis: Autoimmune hyperthyroidism (Graves' disease) is associated with advanced skeletal maturation and rapid growth. However, the final height is almost normal.

McCune–Albright syndrome: The condition is associated with somatic activating mutation of the *GNAS1* gene. The classical triad of this condition is café au lait spots, peripheral precocious puberty, and fibrous tall stature. It is also associated with GH excess (acromegaly), Cushing syndrome, and thyrotoxicosis. Tall stature is due to pituitary gigantism.

Assessment

Critical aspects of evaluating a child with tall stature include its confirmation, differentiation of physiological from pathological causes, and establishment of cause (*see* **Flowchart 1**).

Is it tall stature?: Tall stature is diagnosed with a height SDS above 2, height velocity above 90th percentile, or upward crossing of two or more major percentile lines between 2 years and puberty.

Is it physiological or pathological?: Corrected height SDS below +1.5 indicates familial form; tall stature in only

one parent suggests an autosomal dominant disorder like Marfan syndrome. Increased growth after 4 years of age with advanced bone age and normal predicted adult height suggests a constitutional cause. Normal bone age and increased predicted adult height point to familial tall stature.

What is the cause?: Increased birth weight suggests overgrowth disorders (BW, Simpson Golabi, and Sotos syndromes). Pointer to etiology should be assessed. Large head size indicates Sotos syndrome and GH excess, while dolichocephaly is observed in Marfan syndrome. Beckwith–Wiedemann syndrome is characterized by asymmetry, omphalocele, and ear creases. GH excess should be considered with teeth separation, mandibular prognathism, thick heel, large hand and feet, and neuropathy. Pointers on the general examination such as pectus carinatum (Marfan syndrome, homocystinuria), gynecomastia (Klinefelter syndrome, aromatase excess), café-au-lait spots (MAS, neurofibromatosis type 1), lentigines (Carney complex), and ear crease (BWS) should be examined. Eye examination for lens position (superior dislocation is Marfan syndrome and inferior dislocation in homocystinuria) is vital.

Growth hormone axis should be assessed only after excluding physiological and syndromic causes. Basal GH is of limited value, although levels <0.4 ng/mL make GH excess unlikely. IGF1 levels above +2 SDS for age and gender indicate GH excess and should be confirmed by a GH suppression test (GH levels >1 ng/mL 2 hours after 1.75 g/kg oral glucose). Genetic evaluation should be done per clinical features (NSD1 with a large head and clumsiness; fibrillin with arachnodactyly, pectus deformity; cystathionine β-synthase with thrombosis and ectopia lentis, and karyotype with tall stature and stalled puberty).

Management

Most cases do not need treatment to limit final height. The only two treatment modalities to limit final height are high-dose sex steroids and epiphysiodesis. Indications to limit final height are when predicated adult height is 3 SD above the mean or significant psychosocial impairment.

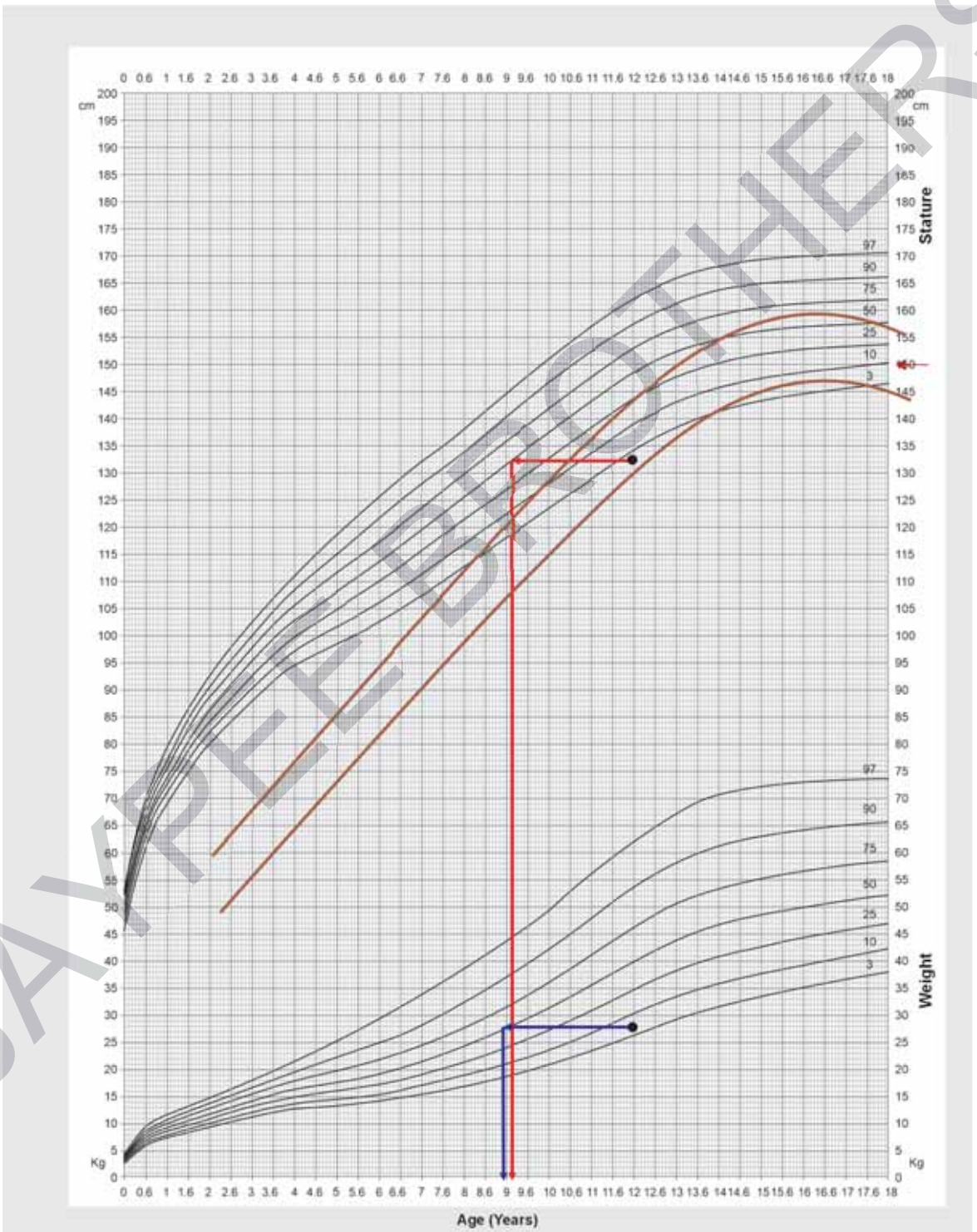
High dose sex steroids: High dose estradiol (100–200 μg/day) in girls and high dose testosterone (200–500 mg every 2 weeks by deep intramuscular injection) limit final height by rapid fusion of epiphysis. It should be given for 6 months or till the cessation of growth. The therapy reduces the predicted final size by 5–10 cm but is associated with side effects such as hypertension, menstrual irregularity, acne, dyslipidemia, and thromboembolism.

Epiphysiodesis involves surgical destruction of the growth plate around the knee joint, preventing further linear growth. It is not recommended currently.

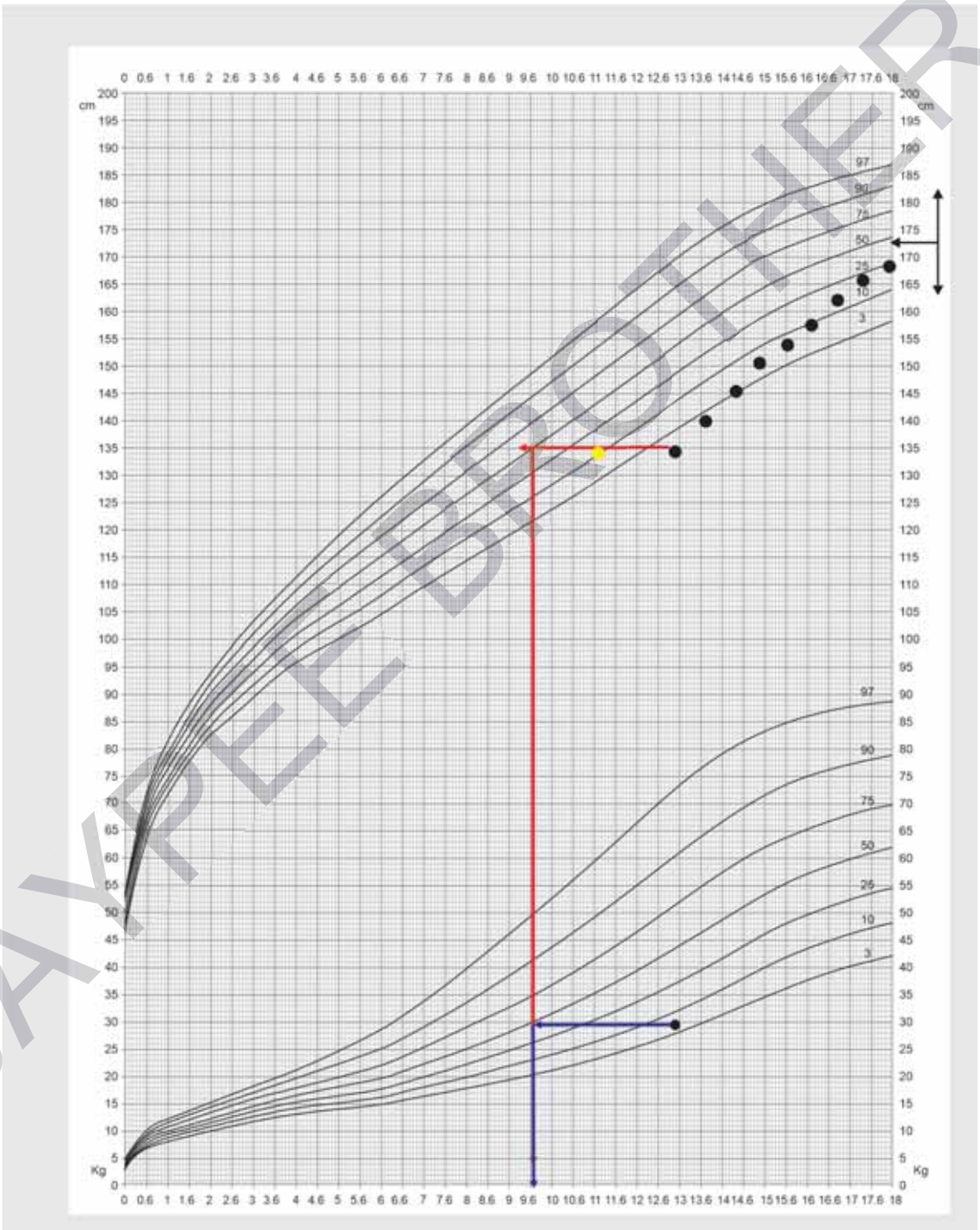
Management of pituitary gigantism: Definitive treatment is the surgical removal of the tumor. Medical management includes octreotide; somatostatin receptor analog suppresses GH secretion. Pegvisomant, a selective antagonist of the GH receptor, prevents GH action.

CASE SCENARIOS

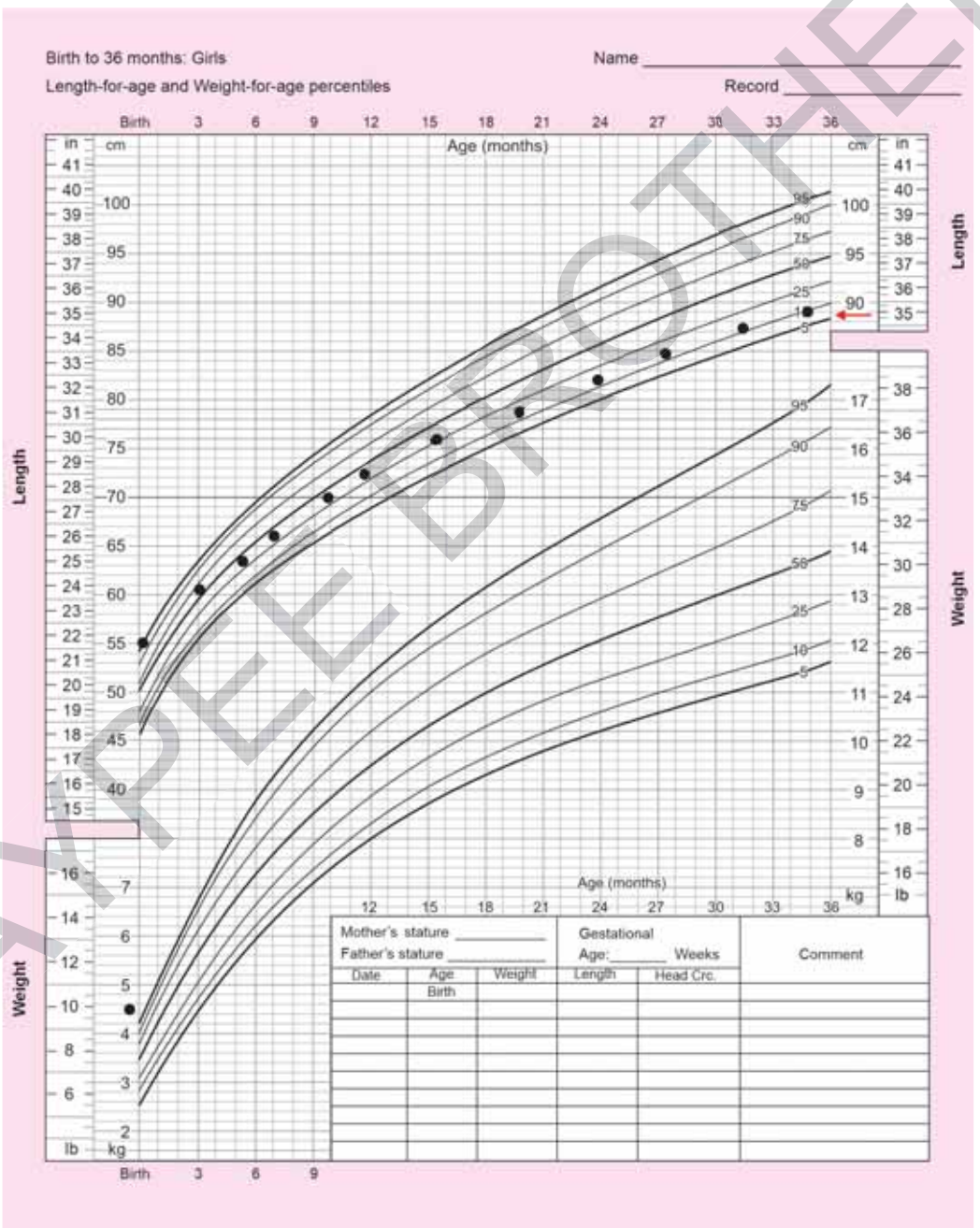
Case 1: A 12-year-old girl with a height of 132 cm and weight 12 kg for work-up. The child is below the third centile for height but within parental range. Both height age and weight age are 9 years. Low height percentile with height in the parental range suggests familial short stature. On follow-up at 6 months, she grew by 3.5 cm indicating normal growth.



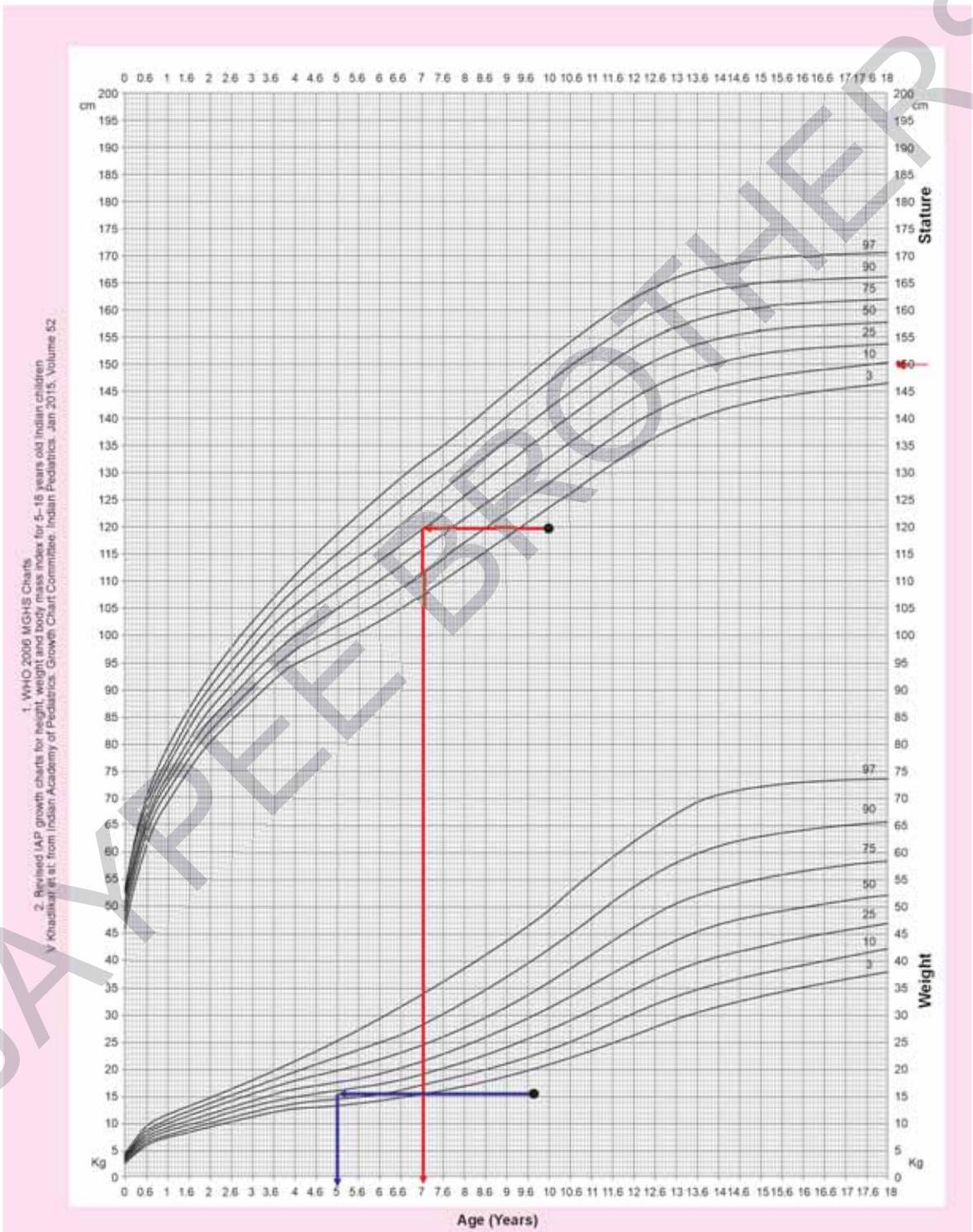
Case 2: A 13-year-old boy with a height of 135 cm and weight of 30 kg was diagnosed with GHD. The boy had height and weight below the third percentile and parental expectations. Screening tests were normal. GHD was diagnosed after a growth hormone (GH) stimulation test showed a peak GH of 3.2 ng/mL. Key aspects to assess include pubertal status and bone age as the severity of growth failure is more in line with constitutional delayed puberty and growth and not GHD. The child was prepubertal with a bone age of 11 years. The GH test was done without priming. Repeat testosterone-primed GH test showed a peak value of 15.2 ng/mL excluding GHD. On follow-up, the child grew at a normal rate achieving parental expectations.



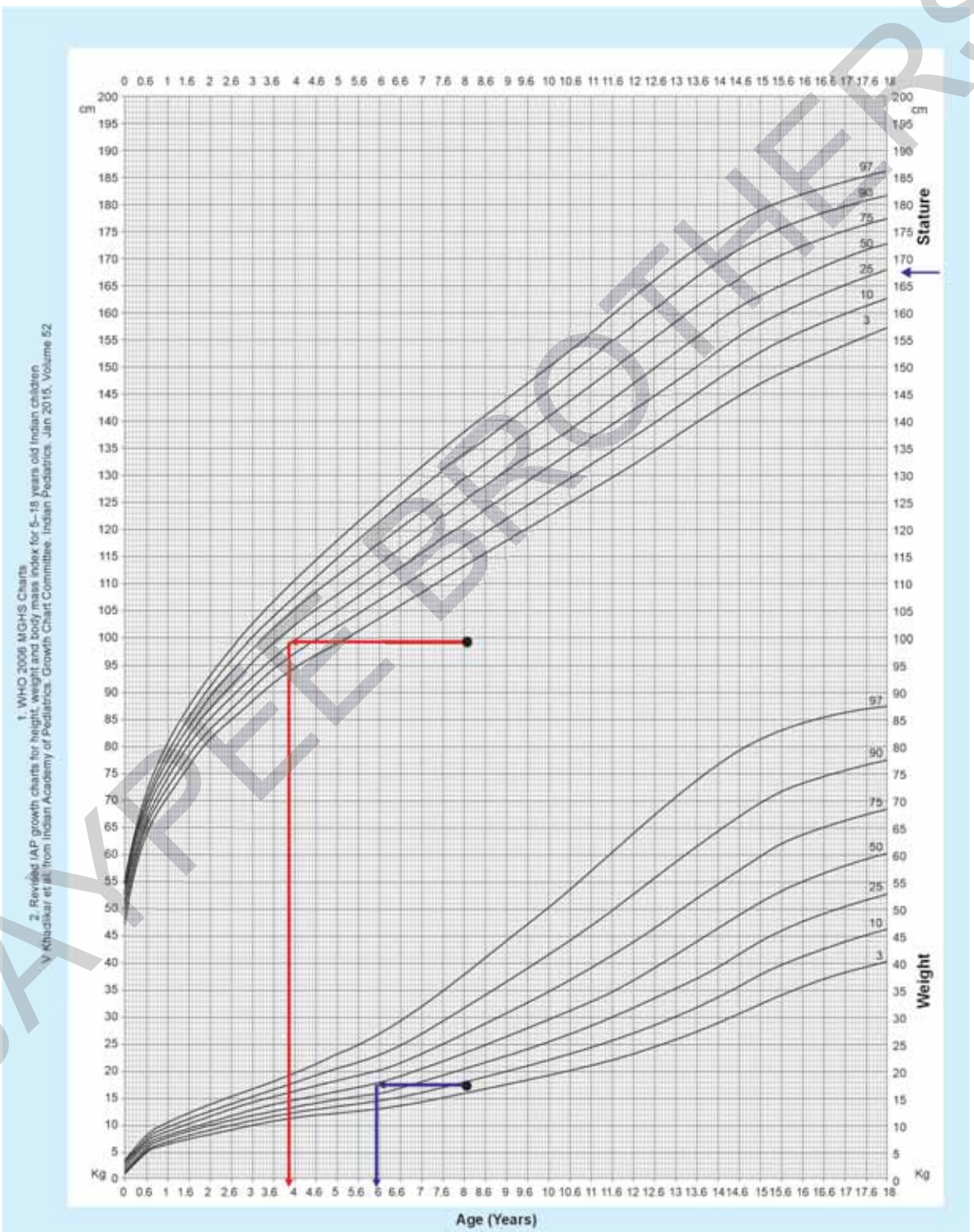
Case 3: A 15-month girl with failure to thrive was diagnosed as renal tubular acidosis. This girl was born with a birth weight of 4,000 g. Over follow-up, the child crossed multiple percentile lines to the 10th percentile by 15 months of age. Work-up at this point showed mild metabolic acidosis (base excess of –7 mmol/L) prompting the diagnosis of RTA. The severity of growth failure is, however, not commensurate with RTA where greater growth retardation is expected. It is important to identify the cause of increased birth weight in the child along with parental expectations. History revealed that the child was born to a diabetic mother with a mid-parental expectation at the third percentile. This child represents the classical impact of environment and genetics on growth. Thus, while size at birth is determined by environment that at final height is regulated by genetics. The switch from the environment to genetics happens by 2 years of age with catch-up or catch-down growth commensurate with parental expectation. Thus, changes in growth trajectory in this period in accordance with parental expectations are not indicative of disease. This child had compromised genetic potential and was born large at birth due the maternal diabetes mellitus. This postnatal growth deceleration is not a cause of concern and the work-up was not required.



Case 4: A 10-year-old girl with a height of 120 cm and weight of 15 kg was diagnosed as GHD. This girl had normal screening tests including TTG. GH deficiency was diagnosed based on low IGF1 and basal GH levels. However as seen from the growth chart, weight is more affected than height suggesting nutritional cause. She gave a history of pica and anemia. IgA levels were assessed due to high suspicion of celiac disease and were low. Biopsy was suggestive of subtotal villous atrophy. Gluten-free diet resulted in dramatic improvement.



Case 5: An 8-year-old boy with a height of 100 cm and weight 18 kg was diagnosed as celiac disease. Celiac disease was diagnosed as TTG levels were increased (32 IU/L). He was started on gluten-free diet without a duodenal biopsy. He was referred in view of no response to gluten-free diet. As seen in the growth chart height is more affected than weight suggesting an endocrine pattern of growth failure. GH stimulation test showed complete GHD with excellent response to GH therapy.



Case 6: A 14-year-old-boy with tall stature and chest pain. This boy had tall stature (height 184 cm) with arachnodactyly, pectus carinatum, and increased arm span indicating Marfan syndrome. He presented 3 years later with acute chest pain. This, in the setting of Marfan syndrome, suggested aortic dissection that was confirmed on MRI.

Case 7: A 13-year-old girl with tall stature, lens dislocation, and hemiparesis. This girl presented with left-side hemiparesis. On examination, she was tall (height of 174 cm with a target height of 156 cm) with inferior lens dislocation. Cerebrovascular accident, tall stature, and ectopia lentis suggest homocystinuria. Further work-up should include homocysteine levels and genetic analysis for cystathionine β-synthase.

KEY POINTS

- Growth chart and anthropometry assessment are the cornerstone in diagnosis abnormalities of stature (short or tall stature).
- Bone age and pubertal assessment are very helpful in differentiating physiological and pathological causes of abnormal stature. The children with mildly delayed bone age, puberty and growth are likely to have constitutional delay of growth and puberty, careful follow-up is wise before doing extensive laboratory work-up.
- A judicious and step wise approach can help reach final diagnosis.
- Timely identification of pathological causes and their timely management can prevent abnormal stature in adult life.

SUGGESTED READING

1. Bajpai A, Agarwal N. Growth failure. In: Bajpai A, Patel R, Dave C, Agarwal N (Eds). MedEClasses Pediatric Endocrinology. Kanpur: Grow Society Publication; 2019; pp. 49-53.
2. Bajpai A, Dave C. Growth hormone therapy. In: Bajpai A, Dave C, Agarwal N, Patel R (Eds). MedEClasses Textbook of Pediatric Endocrinology: Basic Pediatric Endocrinology, 1st edition. MedEClasses; 2019. pp. 55-64.
3. Bajpai A. Tall stature. In: Bajpai A (Ed). Advanced Pediatric Endocrinology, Volume I. 1st edition. MedEClasses; 2021. pp. 175-82.
4. Collett-Solberg PF, Ambler G, Backeljauw PF, Bidlingmaier M, Biller BMK, Boguszewski MCS, et al. Diagnosis, genetics, and therapy of short stature in children: A Growth Hormone Research Society International perspective. Horm Res Paediatr. 2019;92(1):1-14.
5. Cooke DW, Divall SA, Redovick S. Normal and aberrant growth in children. In: Melmed S, Auchus RJ, Goldfine AB, Koenig RJ, Rosen CJ (Eds). Williams Textbook of Endocrinology. 14th edition. Philadelphia: Elsevier; 2020. p. 941.
6. Euling SY, Herman-Giddens ME, Lee PA, Selevan SG, Juul A, Sørensen TI, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. Pediatrics. 2008;121(Suppl 3):S172-91.
7. Farooqi IS, O'Rahilly S. 20 years of leptin: human disorders of leptin action. J Endocrinol. 2014;223(1):T63-70.
8. Gan HW, Alatzoglu K, Dattani MT. Disorders of the hypothalamic-pituitary axis. In: Dattani MT, Brook CGD (Eds). Brook's Clinical Pediatric Endocrinology. 7th edition. London: Wiley Publishers; 2019. pp. 131-74.
9. Goede J, Hack WW, Sijstermans K, van der Voort-Doedens LM, Van der Ploeg T, Meij-de Vries A, et al. Normative values for testicular volume measured by ultrasonography in a normal population from infancy to adolescence. Horm Res Paediatr. 2011;76(1):56-64.
10. Goodman RL, Lehman MN, Smith JT, Coolen LM, de Oliveira CV, Jafarzadehshirazi MR, et al. Kisspeptin neurons in the arcuate nucleus of the ewe express both dynorphin A and neurokinin B. Endocrinology. 2007;148(12):5752-60.
11. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, et al. EDC-2: The Endocrine Society's second scientific statement on endocrine-disrupting chemicals. Endocr Rev. 2015;36(6):E1-150.
12. Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017;177(3):G1-70.
13. Grimberg A, DiVall SA, Polychronakos C, Allen DB, Cohen LE, Quintos JB, et al. Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency. Horm Res Paediatr. 2016;86(6):361-97.
14. Hokken-Koelega ACS, van der Steen M, Boguszewski MCS, Cianfarani S, Dahlgren J, Horikawa R, et al. International Consensus Guideline on Small for Gestational Age (SGA): Etiology and Management from Infancy to Early Adulthood. Endocr Rev. 2023;44(3):539-65.
15. Kaiser U, Ho K. Pituitary physiology and diagnostic evaluation. In: Melmed S, Auchus R, Goldfine A, Koenig R, Rosen C, Auchus RJ, et al. (Eds). Williams Textbook of Endocrinology. 14th edition, Manesar: Elsevier; 2019. pp. 184-235.
16. Khadilkar V, Kondpalle S, Normal growth. In: Khadilkar V, Bajpai A, Prasad HK (Eds). IAP Textbook on pediatric endocrinology. 1st edition. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2019. p. 37.
17. Murray PG, Clayton PE, Disorders of growth. In: Dattani M, Brook CGD (Eds). Brook's Clinical Pediatric Endocrinology. 7th edition. India: Wiley-Blackwell; 2019. p. 201.
18. Patel R, Bajpai A. Evaluation of short stature in children and adolescents. Indian J Pediatr. 2021;88(12):1196-202.
19. Ranke M, Reiter EO, Price DA. Idiopathic growth hormone deficiency in KIGS: selected aspects. In: Ranke M, Price DA, Reiter EO (Eds). Growth Hormone Therapy in Pediatrics: 20 Years of KIGS. 1st edition. Basel: Karger; 2007. pp. 116-35.

Textbook of
Growth, Development & Behavioral
PEDIATRICS

Salient Features

- Highly informative, updated textbook recommended for undergraduates, postgraduates, and consultant pediatricians
- Includes five sections and over 53 chapters
- Comprehensive approach to growth disorders, along with latest IAP growth charts
- Approach and management of developmental disabilities
- Guidelines for identification and management of common behavioral problems
- Exclusive section on early intervention strategies in office practice
- Ready to use charts and assessment tools
- Chapters contributed by experts in growth, development, and behavioral pediatrics along with experts in allied specialties and rehabilitation professionals from all over India.

Chief Editors

Anjana Thadhani
MBBS DCH DNB FCPS PGD Developmental Neurology PGD Juvenile Jurisprudence
Consultant Developmental Pediatrician
Department of Pediatrics

Learning Disability Clinic, KEM Hospital and Niramay Guidance Clinic
Mumbai, Maharashtra, India

Chairperson
IAP Growth, Development and Behavioral Pediatrics Chapter (2020–2021)

Ashok Rai
MD PhD FIAP FNNF FIAMS FACI Fellowship in Genetics Fellowship in Allergy and Immunology
Director
Indian Institute of Cerebral Palsy and Handicapped Children
Varanasi, Uttar Pradesh, India

Chairperson, IAP Growth, Development and Behavioral Pediatrics Chapter (2018–2019)

Chairperson, IAP Infectious Diseases Chapter (2017)
National Vice President, Indian Academy of Pediatrics (2013), Indian Medical Association (2021)

Secretary General, Indian Academy of Health Psychology (2019–2024)

Hon Professor, Indian Medical Association and IMA Academy of Medical Specialties

Academic Editor

Jaydeep Choudhury MBBS DNB (Ped) MNAMS FIAP
Professor
Department of Pediatrics

Institute of Child Health
Kolkata, West Bengal, India

Chairperson, IAP Growth, Development and Behavioral Pediatrics Chapter (2022–2023)

National Vice President, Indian Academy of Pediatrics (2019)

Associate Editors

Suchit Tamboli
PhD FIAP MBBS DCH PGDAP PGDMLS
Director and Consultant Developmental Pediatrician
Department of Pediatrics

Chiranjiv Clinic and Child Development Research Institute, Ahmednagar, Maharashtra, India

Chairperson, IAP Growth and Development Academy (2014–2015)

Suneel Godbole MBBS MD (Pediatrics)
Consultant Developmental Pediatrician and Head

Chiranjeev Child Diet and Development Centre
Deenanath Mangeshkar Hospital and Research Center, Pune, Maharashtra, India

Secretary, IAP Growth, Development and Behavioral Pediatrics Chapter (2022–2023)

President, IAP Growth, Development and Behavioral Pediatrics Chapter (2024–2025)

Amola Patel MBBS DCH PGDDN
Consultant Developmental Pediatrician

Aashay Early Intervention Center
Ahmedabad, Gujarat, India

Vice Chairperson, IAP Growth, Development and Behavioral Pediatrics Chapter (2022–2023)

Secretary, IAP Growth, Development and Behavioral Pediatrics Chapter (2024–2025)

Printed in India

Available at all medical bookstores or buy online at www.jaypeebrothers.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
EMCA House, 23/23-B, Ansari Road, Daryaganj, New Delhi - 110 002, INDIA
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers

Shelving Recommendation
PEDIATRICS

ISBN 978-93-5696-799-1