

CHAPTER 1

Growth

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Overview

- Introduction
- Growth Monitoring: Basics of Growth
 - Recommendations for Growth Monitoring
 - Techniques of Height/Length Measurement
 - Height
 - Length
 - Techniques of Weight Measurement
 - Plotting of Growth Chart
 - Interpretation
 - Other Important Parameters for Assessment of Growth
- Approach to Short Stature
 - Short Stature
 - Growth
 - Phases of Growth
 - Laboratory Studies
 - Management
- Growth Hormone Deficiency
 - Molecular Genetics of Growth Hormone Deficiency
 - IGF-I and IGF-IR Mutations
 - Clinical Presentation
 - Presentation with Congenital Deficiency
 - Presentation with Acquired Deficiency
 - Consideration and Diagnosis of GHD
 - Growth Hormone Therapy
- Growth Hormone Resistance/Growth Hormone Insensitivity
 - Classification of Growth Hormone Resistance
 - Diagnosis
 - Genetic Studies
 - Treatment
- Other Causes of Short Stature
 - Turner Syndrome
 - Etiology
 - Clinical Presentation
 - Diagnosis and Genetics
 - Management
 - Small for Gestational Age
 - Management
 - Silver–Russell Syndrome
 - Management
 - Noonan Syndrome
 - Management
 - Prader–Willi Syndrome
 - Management
 - Idiopathic Short Stature
- Tall Stature
 - Introduction
 - Etiology
 - Approach to Tall Stature
 - Treatment
 - Growth Hormone (GH) Excess
 - Diagnostic Evaluation
 - Treatment
- Key Points

Introduction

Growth can be defined as a gradual process of development in maturity, age, size, weight, or height. Children go through different phases of growth, with each phase having different

characteristics, and so it is important to monitor the growth of all children from birth onward to pick up on early features of faltering.

This chapter on growth entails the basics and tools of growth monitoring, followed by conditions of short stature with growth

hormone (GH) deficiency and nondeficiency. At the end of the chapter we will discuss overgrowth.

● Growth Monitoring: Basics of Growth

Growth is the fundamental physiologic process that characterizes childhood. It should be closely monitored by pediatricians and families alike as a benchmark of a child's health.

Recommendations for Growth Monitoring¹

The Indian Academy of Pediatrics (IAP) advises the following growth monitoring protocol:

- At birth: weight, length, head circumference, and penile length.
- Six weeks to 3 years (weight, length, and head circumference on every visit):
 - ◇ During vaccinations (6, 10, 14 weeks, 9 months, 15–18 months).
 - ◇ Additional visit at 6 months coinciding with any illness.
 - ◇ 6-monthly visits between 18 to 36 months.
- 3–8 years:
 - ◇ 6-monthly height and weight.
 - ◇ Body mass index (BMI).
 - ◇ Sexual maturity rating from 6 years onwards.
- 8–18 years:
 - ◇ On an annual basis, height, weight, BMI, and

Techniques of Height/Length Measurement

Children below the age of 2 years should be measured on an infantometer and above 2 years with stadiometer. Two persons are needed to take length of a child accurately.

Height

1. Measure height for children 24 months and older, if they can stand unassisted.
2. Measure without shoes and wearing light clothing.

3. Remove hair accessories that interfere with measurement.
4. Position child with feet flat and together on the base of the board.
5. Heels, back of the knees, buttocks, shoulder blades, and back of head touch back of board, while child is maintaining a normal stance. For some children, this is not possible and only the heels and buttocks will touch the board. The head should be in the Frankfurt plane (an imaginary line from the lower border of the eye orbit to the auditory meatus) in inspiration.
6. Shoulders level and eyes looking straight ahead.
7. Headpiece firmly against top of the child's head and firmly against the board.
8. Read measurement to the nearest 0.1 cm.
9. Sitting height is measured from the vertex to the base of the seat using a stadiometer. The head, shoulder, and buttocks should touch the surface. The sitting height is then subtracted from the total height to calculate the lower segment.

Length

1. Measure length for children less than 24 months of age.
2. Measure infant without shoes and wearing light underclothing or clean diaper.
3. Remove hair accessories that interfere with measurement.
4. Lay child on his back in the center of the measuring surface.
5. Assistant cups the ears to hold the infant's head, so the infant is looking upward, and the crown of the head is against the headpiece.
6. Bring knees together, extend both legs, and bring movable foot piece to rest against heels.
7. Read measurement to the nearest 0.1 cm.

Techniques of Weight Measurement

Weight should be measured with standard weighing scale and minimum clothing to the nearest 0.01 kg.

Plotting of Growth Chart

Growth charts are graphical representations of statistically adjusted growth data on apparently healthy normal children. Growth charts give changing trend of a variable over time and hence are immensely useful in the diagnosis and follow-up of children with disease.²

Height and weight should be plotted on age, sex, and population-specific growth chart along with target height for correct interpretation. As per the consensus, for Indian population below 5 years of age, WHO growth charts are recommended. For those between 5 to 18 years of age, IAP 2015 charts are recommended;² however, Center for Disease Control and Prevention (CDC) charts and KN Aggarwal charts are also being used in some institutions.

Interpretation

IAP growth charts are recommended for children from 5 to 18 years of age. In case of height charts, any child under 3rd percentile is considered to be abnormally short and above 97th is considered to be abnormally tall. In IAP BMI charts underweight may be defined as below 3rd percentile, risk for overweight as above 23rd percentile adult equivalent, and risk for obesity as above 27th percentile adult equivalent lines.² For children below 5 years of age, WHO charts are recommended.³ However, in any chart trend of growth pattern, crossing of different centile lines (upward or downward) is more important than single measurement.

Other Important Parameters for Assessment of Growth

1. **Upper segment:lower segment (US:LS) ratio:** Sitting height can be measured and subtracting it from standing height yields lower segment. At birth, US:LS is 1.7:1 and gradually decreases to 1.3:1 at 3 years of age. It is 1:1 at approximately 7 years of age and during puberty, it is 0.85–0.9. Lower segment is measured standing using a stadiometer from pubic symphysis to the floor; alternatively, patient's sitting height can also be taken as upper segment and other can be measured by deducting from height. In infants, upper segment is measured by using an infantometer and marking the upper segment by pressing the lower board against buttocks while lifting both feet up. In cases of a taller child, it can be measured by marking the pubic symphysis. Lower segment is measured by subtracting the upper segment from total length.
2. **Arm span:** Arm span is less than height approximately by 3 cm till 7 years of age, then it becomes equivalent to height. During puberty, arm span is more than height; in boys, it is 4 cm more, while in girls, it is 1 cm more.
3. **Tanner pubertal staging³:** Pubertal staging is necessary in all children being assessed for growth.
 - Breast development scale:
 - ◇ Stage 1: No glandular breast tissue palpable.
 - ◇ Stage 2: Breast bud palpable under areola (1st pubertal sign in females).
 - ◇ Stage 3: Breast tissue palpable outside areola; no areolar development.
 - ◇ Stage 4: Areola elevated above contour of the breast, forming "double scoop" appearance.
 - ◇ Stage 5: Areolar mound recedes back into single breast contour, with areolar hyperpigmentation, papillae development, and nipple protrusion.
 - Male external genitalia scale:
 - ◇ Stage 1: Testicular volume < 4 mL or long axis < 2.5 cm.

- ◇ Stage 2: 4–8 mL (or 2.5–3.3 cm long); 1st pubertal sign in males.
 - ◇ Stage 3: 9–15 mL (or 3.4–4.0 cm long).
 - ◇ Stage 4: 15–20 mL (or 4.1–4.5 cm long).
 - ◇ Stage 5: > 20 mL (or > 4.5 cm long).
 - Pubic hair scale (both males and females):
 - ◇ Stage 1: No hair.
 - ◇ Stage 2: Downy hair.
 - ◇ Stage 3: Scant terminal hair.
 - ◇ Stage 4: Terminal hair that fills the entire triangle overlying the pubic region.
 - ◇ Stage 5: Terminal hair that extends beyond the inguinal crease onto the thigh.
4. **Target height:** Target height (TH) or genetic potential is assessed with the help of the following formulas:
- $$[(\text{Father's height} + \text{mother's height}) - 13] / 2 = \text{midparental height (MPH) / TH in girls.}$$
- $$[(\text{Father's height} + \text{mother's height}) + 13] / 2 = \text{MPH/TH in boys.}$$
- Target calculated range (MPH \pm 6.0 cm) is plotted on growth chart to look for short or tall stature.
5. **Bone age assessment:** Bone age (BA) assessment is an important tool of growth assessment. The bone age assessment is done by evaluating the X-ray of the left hand and wrist for skeletal maturation (**Fig. 1.1**). The exact calculations are done by comparing the stages of ossification of the epiphysis and comparing the chronological standards of normal children; a difference of > 2 standard deviation (SD) of the chronological age and bone age is considered abnormal, and described as advanced or delayed bone age, which helps in diagnosing several conditions (**Table 1.1**). Hand radiography should be done with the patient sitting alongside or facing a table and

examined in the PA position. Left hand should be in neutral position with no flexion, extension or deviation, and with palm placed down on the cassette with the fingers extended. Exposure should be 50 to 60 Kvp/2–5mAs and a distance of 100 cm. There are several methods available for bone age calculations:

- Tanner–Whitehouse (TW) method: It is one of the most commonly used methods of bone age assessment. TW2 and TW3 atlas is available where radius-ulna-short bones (RUS), including 1st, 3rd, and 5th metacarpal; carpal bones are assessed to calculate bone age. Each bone is categorized into different stages (A, B, C...I) and a numerical score is given. Total maturity score is calculated and correlated with the bone age separately for males and females. It is more accurate and reproducible when compared to Greulich and Pyle (GP) method.⁴ It is available for smart phones in android and iOS application versions. However, it



Fig. 1.1 X-ray of left hand and wrist, digital X-ray, PA view for bone age. Chronological age: 4.11 years, Tanner–Whitehouse (TW) 2 bone age: 8.7 Years, TW3: 7.8 Years.

Table 1.1 Causes affecting bone age⁷

Delayed bone age			
S. No.	Endocrine causes	Nonendocrine cause	Chromosomal
1	Hypothyroidism	Celiac disease	Turner syndrome
2	Growth hormone deficiency	Chronic malnutrition	Noonan syndrome
3	Diabetes mellitus	Chronic renal diseases	Prader–Willi syndrome
4	Hypoparathyroidism	Medication-steroids	Trisomy 21
5	Cushing's disease	Cystic fibrosis	
6	Addison's disease		
7	Hypogonadism		
Advanced bone age			
S. No.	Endocrine causes	Nonendocrine	Chromosomal
1	Precocious puberty	Obesity (nutritional)	Beckwith–Wiedemann syndrome
2	Constitutional tall stature	Estrogen	Sotos syndrome
3	Hyperthyroidism		McCune–Albright
4	Ovarian tumors		
5	Germ cell tumors		
6	Testicular tumors		

is a time-consuming method and requires practice for correct calculation. It also has inter- and intraobserver variability in calculation.

- Greulich and Pyle (GP) method: It is one of the oldest methods in current use. It uses the Radiographic Atlas of Skeletal Development of the Hand and Wrist by Dr William Walter Greulich. It has standard X-rays of left wrist and hand for both males and females, starting from birth till 18 years for females and 19 years for males, and the bone age is computed by comparing the X-ray of the patient with these reference images. However, disparities have been noted in Asian children bone age calculation, and inter- and intraobserver variation is higher in GP than TW.⁵
- Bone Xpert automated bone age calculator: It is the most prominent

example of a completely automated method. It is most widely used method due to ease of use and no inter- and intraobserver variability in calculation. However, it is not available in many institutes, as it is a paid service, and a minimal amount is charged on every bone age calculation. Bone Xpert takes into account 15 bones of the hand radiographs and computes the bone age by using GP and TW methods.

- Gilsanz and Ratibin (GR) atlas: It was developed by Vicente Gilsanz and Osman Ratibin in 2005. It has more precise and better quality images than the GP atlas. The GR atlas is spaced semiannually for those between 2 to 6 years and annually for those between 7 to 17 years.⁶
- 6. **Height age (HA):** It is the age of the child which corresponds to his height

when plotted at the 50th percentile on a growth chart.

7. **Chronological age:** It is the age of the child calculated from his date of birth.
8. **Weight age (WA):** It is the age of the child that corresponds to his or her weight when plotted at the 50th percentile on a growth chart.
9. **Adult height predictions:** Prediction models are available, which can anticipate the expected adult height a child may achieve. Different prediction models take into account different parameters as mentioned below:
 - Bayley–Pinnaeu method: It calculates using current height, chronological age, and bone age determined with the help of the GP method.
 - The TW2 method: Uses the current stature, chronological age, MPH, pubertal status, and bone age calculated by the TW2 method.
 - The Roche–Wainer–Thissen method: Takes into account the current weight, recumbent length, MPH, and bone age calculated by the GP method.
 - The Khamis–Roche algorithm: Uses a linear correlation of the child's height, weight, along with MPH.
 - The Bone Expert: Uses a formula that takes into account current height,

bone age, chronological age, and both the parents' height.

- I grow: It uses the current height and chronological age, providing yearly height predictions in children treated with GH.
- Multiplier method for height prediction:⁸ Uses a formula of average height multiplier values (M) for boys and girls ($M = Htm/Ht$).
Htm = height at skeletal maturity.
Ht = present height (for each age, gender, and height percentile, using data published by the CDC).

It is important to plot the bone age, WA, and HA of a child against the chronological age, as they give valuable information in predicting the underlying etiology (**Table 1.2**).

A detailed systematic evaluation should be done in all children, and every child should be plotted on a growth chart against the MPH, as it may provide the first clue to a child with growth faltering.

Approach to Short Stature

Short Stature

A child who is 2 SD or more below the mean height for children of that sex, chronologic age, and racial-ethnic group is described as having short stature.⁹ Assessment of growth over a period of time, showing progressive deviation

Table 1.2 Approach to several growth disorders on basis of bone age, chronological age, height age, and weight age

Formula		Interpretation
$CA > HA > WA$	BA minimally affected	Malnutrition Chronic illness
$BA > HA > CA$		Precocious puberty
$WA > CA > HA$	BA may be delayed	Cushing's
$CA < HA < WA$	BA may be advanced	Exogenous obesity
$CA > HA = BA$	BA may be delayed up to 2 years	CDGP
$HA < BA = CA$		Familial short stature

Abbreviations: BA, bone age; CA, chronological age; CDGP, constitutional delay in growth and puberty; HA, height age; WA, weight age.

from a growth percentile (or growth curve), is far more important than single measurement of height.

Growth

Growth is one of the most important parameter of monitoring child's well-being. Families and pediatricians should monitor it. The recommendations of IAP for growth monitoring have been discussed already.

Phases of Growth

Statural growth is a continuous process but it is not linear. There are three phases of post-natal growth where different factors influence each phase.¹⁰ It is important to understand each phase in order to identify the etiology. These phases are similar for both male and females, however, timing and pace of growth differ, especially during puberty.

Infantile Phase

It constitutes the initial 2 years of life. There is a rapid but decelerating growth, consisting of overall growth of about 30 to 35 cm during this period. Infants may cross percentile lines during this phase, as they grow toward the genetic potential, showing catch up or catch down growth, depending upon excesses or constraints of the intrauterine environment. Hormones do not influence much on this phase of growth, and it is mainly nutrition oriented.¹¹

Childhood Phase

It starts following the infantile phase and is characterized by a relatively constant growth velocity of 5 to 7 cm per year in both sexes until pubertal phase starts; there is often slight slowing later in childhood just before puberty. It is under the influence of mainly GH and thyroid hormone, and children with GH deficiency usually present in this age.¹¹

Pubertal Phase

It is characterized by a growth spurt of 8 to 14 cm per year and mainly under the influence of increasing gonadal steroid and GH secretion.¹²

Etiological classification of short stature is as follows:¹³

- Normal:
 - ◇ Constitutional growth delay.
 - ◇ Genetic/familial.
- Pathological:
 - ◇ Psychosocial growth retardation.
 - ◇ Nutritional:
 - Rickets.
 - Hypocaloric/hypoproteinemic.
 - ◇ Endocrine:
 - GH deficiency.
 - Hypothyroidism.
 - Pseudohypoparathyroidism.
 - Hypercortisolemia.
 - Precocious puberty.
 - Poorly controlled type 1 diabetes.
 - ◇ Chromosomal defects:
 - Turner's syndrome.
 - Down's syndrome.
 - ◇ Small for gestational age with failure to catch up.
 - ◇ Skeletal dysplasias.
 - ◇ Gastrointestinal, cardiac, renal, and pulmonary chronic lung diseases.

Evaluation of a child suspected of having short stature is guided by answering the following:

1. **Historical details:**
 - Whenever possible, previous growth velocity and duration of growth faltering should be obtained.
 - Specific symptoms pertaining to chronic illness.
 - i. Polyuria (renal tubular acidosis, chronic renal insufficiency, diabetes insipidus).
 - ii. Chronic diarrhea, greasy stools (malabsorption, chronic inflammatory bowel disease).
 - iii. Headache, vomiting, visual problems (pituitary/hypothalamic/cranial space occupying lesions, e.g., craniopharyngioma, pituitary adenoma, etc.).
 - iv. Lethargy, constipation, weight gain (hypothyroidism, hypercortisolemia).

- v. Fatigue (renal tubular acidosis).
 - vi. Altered bowel habits, weight loss (malabsorption, celiac disease).
 - vii. Psychomotor retardation (hypothyroidism).
- Neonatal period: history of poor weight gain/loss, difficulty in feeding, hypoglycemia, any features suggestive of hypopituitarism (neonatal jaundice, constipation, micropenis, single incisor, midline defect), and congenital hypothyroidism.
 - Past history of any surgical or medical treatment (inhaled/topical steroids, substance abuse).
 - Family history: history of consanguinity, age of maternal menarche, any history of delayed puberty in either of the parents, any significant history of short stature in the family, history of any maternal illness, drug use, alcohol use, any history of emotional deprivation, resulting in psychosocial dwarfism, home atmosphere.
 - Nutrition history, dietary habits.
 - Signs of early puberty: Mood swings, sweating, body odor, vaginal discharge, growth spurt, change in dress or shoe size, increase in breast, or penis growth.
2. **Examination details:** These are listed in **Table 1.3**.
 3. **Confirm short stature:** Measure height along with parent's height with proper technique and tools as described earlier. Plot height and target height and target range for that family in age, sex and, preferably, racial ethnicity specific growth chart to rule out familial short stature.
 4. **Disproportionate/proportionate short stature:** The upper segment and lower segment should be measured, and the ratio compared to diagnose disproportionate short stature.¹⁴ Shortening of spine is diagnosed by measuring the sitting height:
 - Conditions of increased upper segment > lower segment include achondroplasia (most common), osteogenesis imperfecta, hypochondroplasia, multiple epiphyseal dysplasia, Ellis-van Creveld syndrome, metaphyseal chondrodysplasia, and thanatophoric dwarfism.
 - Conditions with upper segment < lower segment are as follows: mucopolysaccharidosis (commonly seen), spondyloepiphyseal dysplasia, metaphoric dwarfism, mucopolipidosis, caries of the spine, Pott's spine, and hemivertebrae.
 5. **Delayed or advanced bone age:** Bone age should be calculated using appropriate atlas for children being evaluated for short stature as described in earlier in the chapter. For children with delayed or accelerated growth, the child's height should be adjusted to the appropriate height percentile, based upon the child's bone age rather than chronologic age. This permits more accurate determination of whether the child is growing appropriately for his or her genetic potential.
 6. **Growth velocity:** Establishing the presence of growth failure requires an accurate plot of the results of multiple measurements of length or height. Children should grow at a rate of at least 5 cm per year from age 4 years until the onset of puberty. In constitutional delay of growth, growth velocity tends to be slow between 6 months and 3 years of age and then normalizes.
 7. **Weight for height or BMI:** If the child is underweight for height, one is more likely to find malnutrition, either primary or secondary to systemic illness. The malnutrition may be a result of

Table 1.3 Head-to-toe examination in a case of short stature

Organ	Features	Aetiology
Head	Large anterior fontanelle	Achondroplasia
		Osteogenesis imperfecta
		Hypothyroidism
		MPS
		Microcephaly in syndromic short stature
		Intrauterine infections
Face	Immature facies	GH deficiency
		Hypothyroidism
		Deprivation syndrome
	Abnormal facies	Turner's syndrome
		Russel–Silver syndrome
		Noonan syndrome
Eyes	Cataract and corneal clouding	Intrauterine infections, mucopolysaccharidosis
	Blue sclera	Osteogenesis imperfecta
Teeth	Delayed dentition	Rickets
		Hypothyroidism
		GH deficiency
	Enamel defects	MPS
Neck	Webbed neck, shield-like chest	Turner's stigmata
	Goiter	
Limbs	Deformity	Skeletal dysplasia, rickets, MPS
	Clubbing, angulation	Skeletal dysplasia,
Skin	Dry skin, myxedema	Hypothyroidism
Genitalia	Sexual maturity rating	
	Cryptorchidism	Noonan syndrome

Abbreviations: GH, growth hormone; MPS, mucopolysaccharidosis.

anorexia, malabsorption, diarrhea, or excess energy expenditure. These children should be evaluated for the presence of gastrointestinal (e.g., celiac or inflammatory bowel disease), cardiac, pulmonary (e.g., asthma or cystic fibrosis), and renal disease. HIV infection should also be considered. Children with endocrine disorders such as Cushing's

syndrome, GH deficiency, and hypothyroidism are usually overweight for height. Endocrine causes of underweight for height are seen in Addison's disease and early hyperthyroidism and diabetes.

- Gender bias:** More boys than girls are referred for evaluation, and boys are referred earlier and for less severe height deficits than girls.

Laboratory Studies

The following laboratory studies are indicated to establish the etiology of short stature:^{9,15}

1. Complete blood count (CBC) and erythrocyte sedimentation rate (ESR): anemia in inflammatory bowel disease, celiac disease, renal failure, chronic illness, raised ESR in inflammatory bowel disease and juvenile rheumatoid arthritis.
2. Electrolytes, creatinine, bicarbonate: renal tubular disorder (electrolyte imbalance, acidosis), renal failure (high creatinine), and Bartter syndrome (hypokalemic alkalosis with hypercalciuria).
3. Calcium, phosphate, alkaline phosphatase: Metabolic bone disease.
4. Liver function test (LFT): Chronic liver disease.
5. Thyroid-stimulating hormone (TSH), free thyroxine (T4): Hypothyroidism.
6. Insulin-like growth factor (IGF-I): GH deficiency, growth hormone insensitivity.
7. Tissue transglutaminase (IgAtTG) or other serological screen for celiac disease.
8. Karyotype in all girls to rule out Turner syndrome, and in boys with associated genital abnormalities.
9. Bone age: Constitutional delay in growth and puberty (CDGP).
10. Additional testing is appropriate if the history and physical examination suggest a particular diagnosis, such as delayed or precocious puberty (luteinizing hormone [LH], follicle-stimulating hormone [FSH], estradiol/testosterone, luteinizing hormone releasing hormone [LHRH] stimulation test), endocrine (cortisol, prolactin), skeletal (skeletal survey), or syndromic cause (genetic study: karyotype/microarray/targeted gene panel using next-generation sequencing [NGS]) of growth failure as described above. Patients with reduced height velocity and/or low IGF-I and

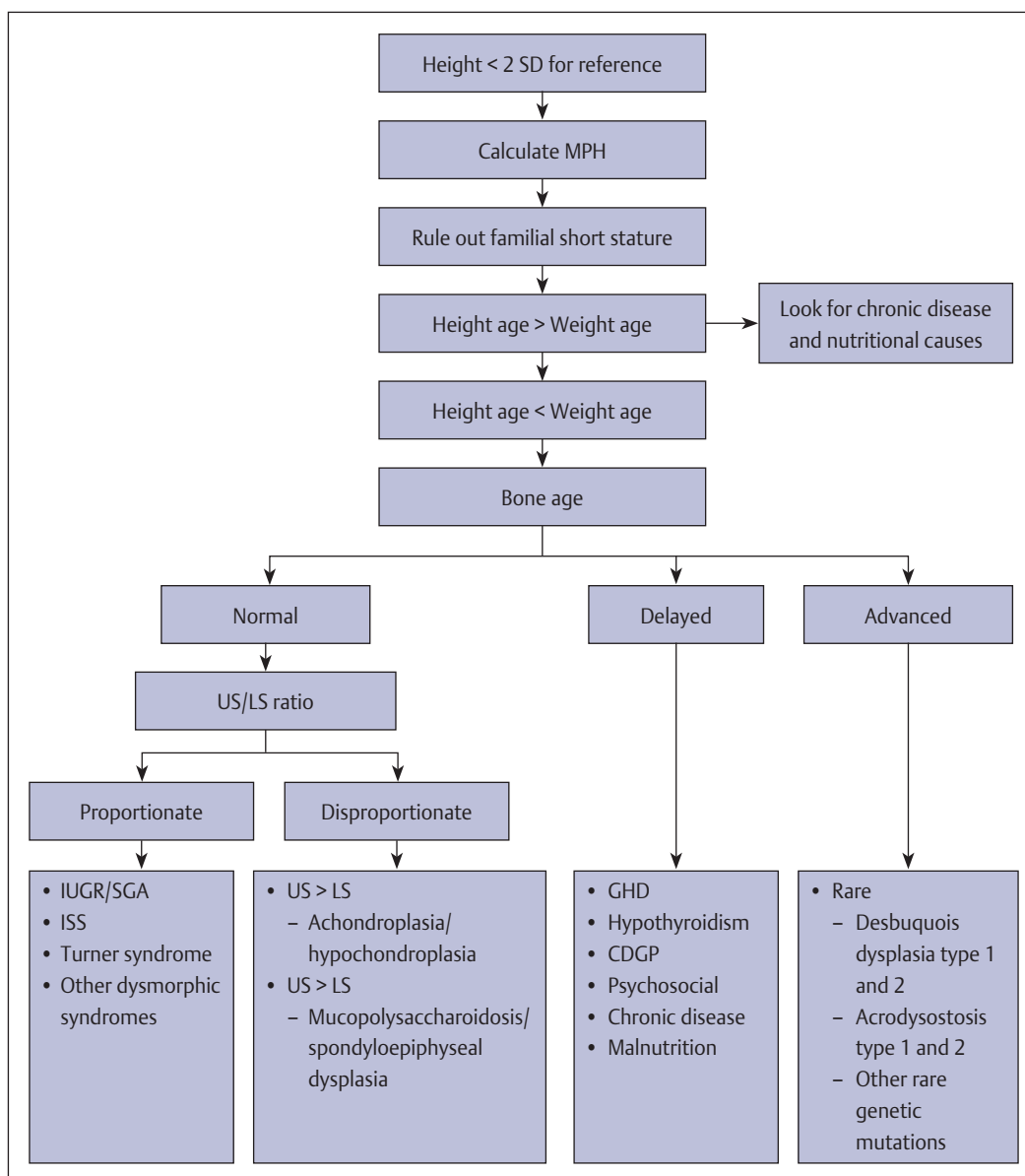
insulin-like growth factor binding protein 3 (IGFBP-3) and delayed bone age should be evaluated for GH deficiency using provocative tests as described in a separate chapter on GH deficiency.

11. Contrast-enhanced MRI of the brain is not necessary to establish the diagnosis of idiopathic short stature, but is appropriate for children with established GH deficiency, or in those with signs or symptoms suggesting hypothalamic-pituitary dysfunction, for example, hypoglycemia, microphallus, cryptorchidism, septo-optic dysplasia, intracranial tumor, or history of cranial irradiation.
12. Genetic testing is not indicated for all children with short stature, however, it should be utilized in diagnostics of specific group of children whose phenotype is suggestive of high probability of mutation.

Management

Short stature is a commonly overlooked complaint in a busy pediatric clinic. Management of any case with short stature depends upon the cause. Children with familial short stature need only reassuring, while children with CDGP need close monitoring. GH has limited indications, which will be described in later chapters. Any patient with short stature should not be overlooked and should be evaluated and managed accordingly, as growth is an important indicator of well-being of the child.

The pediatricians should detect short stature during regular growth monitoring and assess accordingly. The most important step is plotting of weight and height in growth chart during each patient visit. Any patient with malnutrition and underlying systemic disorder needs prompt therapy. Normal variants of short stature such as familial short stature and CDGP are far more common than endocrinological causes of short stature. Each case of short stature should undergo a proper evaluation and assessment (**Flowchart 1.1**).



Flowchart 1.1 Algorithmic approach for clinical evaluation of short stature. Abbreviations: CDGP, constitutional delay in growth and puberty; GHD, growth hormone deficiency; IUGR, intrauterine growth retardation; ISS, idiopathic short stature; LS, lower segment; MPH, midparental height; SD, standard deviation; SGA, small for gestational age; US, upper segment.

☑ Growth Hormone Deficiency

The incidence of short stature associated with growth hormone deficiency (GHD) is described as 1:4000 to 1:10000.¹⁶ GH is the treatment of

choice in GHD. It is administered as daily subcutaneous (SC) injections and costs a substantial amount, which in the Indian scenario is borne entirely by the patients; hence, mandating the need for an accurate diagnosis.^{17,18}

Molecular Genetics of Growth Hormone Deficiency

As many as 3 to 30 percent of children with GHD have an affected parent, sibling, or child.^{19,20} Use of genetic tests should be undertaken judiciously, taking into account family history. The POU1F1 gene is responsible for pituitary-specific transcription of genes for GH, prolactin, thyrotropin, and the growth hormone releasing hormone (GHRH) receptor.^{21,22} Prop-1 mutations result in failure to activate POU1F1/Pit-1 gene expression and probably cause pituitary hypoplasia and/or familial multiple pituitary hormone deficiency.^{23,24} In addition to POU1F1/Pit-1 and Prop-1, other transcription factors participate in the differentiation of anterior pituitary cells, including LHX3, LHX4, TBX19 (TPIT), SOX3, SOX2, and HESX1.⁹ Children with GHRH receptor gene defects have undetectable GH release, but they respond to GH treatment. GH-1 is the gene encoding GH, and mutations of the GH-1 gene have been described as causes of familial GHD.²⁵

Four types of Isolated GH deficiency (IGHD) has been described.

IGHD type 1A: It results from large deletion along with micro-deletion and single base pair substitution of GH1 gene/heterozygous deletion of both alleles of GH1 gene. It can lead to growth retardation in infancy and subsequent dwarfism. It is also frequently associated with development of exogenous GH antibodies.

IGHD type 1B: It results from mutation/rearrangements of GH1 gene. It leads to a less severe form.

IGHD type 2: It is an autosomal dominant condition and also considered the most common form of IGHD.

IGHD type 3: It is partial GH deficiency with X-linked inheritance.

IGF-I and IGF-IR Mutations

These are rare conditions, and patients with IGF-I gene deletion have extremely low levels of IGF-I. These cases present with severe prenatal and

postnatal growth failure, intrauterine growth retardation (IUGR), bilateral sensorineural deafness, moderately delayed motor development, mental retardation, and behavioral difficulties.

Clinical Presentation

GHD may be congenital or acquired. Growth failure is the most common and sometimes the only presentation of GHD, which may sometimes not be manifested until late infancy; hence, accurate documentation of growth rate is imperative to make the correct diagnosis.

Presentation with Congenital Deficiency

Patients with congenital, severe GHD have only a slightly reduced birth length and may not immediately show growth failure. There is a higher frequency of breech presentation and perinatal asphyxia. Neonatal morbidity may include hypoglycemia and prolonged jaundice.

When GHD is combined with deficiency of adrenocorticotrophic hormone (ACTH), hypoglycemia may be severe. The combination of GHD with gonadotropin deficiency can cause micropallus, cryptorchidism, and hypoplasia of the scrotum.

Postnatal growth is abnormal, and growth failure can occur during the first months of life,²⁶⁻²⁹ but it may not be obvious until 6 to 12 months of age, by which time the growth rate is definitely slow and deviates from the normal growth curve, with length measurements often significantly below the mean. Bone age becomes delayed but is similar to height age, unless there is concurrent hypothyroidism.

Presentation with Acquired Deficiency

Children with acquired GHD present with severe growth failure, delayed bone age, weight/height ratios increased, fat distribution often “infantile,” “doll-like,” or “angel-like” (cherubic) in pattern, and immature face with underdeveloped nasal bridge and frontal bossing. The voice is infantile, and hair growth is sparse and thin. The penis may be small, and puberty is usually delayed.

Consideration and Diagnosis of GHD^{15,30}

1. **Clinical and auxological criteria:** Short stature is defined as height more than 2 SD below the population mean. The testing for GHD in such children should be initiated once all other potential causes of growth failure have been considered and excluded.

Criteria to initiate immediate investigation include the following:

- Severe short stature, which is defined as height more than 3 SD below the mean.
 - Height more than 1.5 SD below the MPH.
 - Height more than 2 SD below the mean and a height velocity over 1 year more than 1 SD below the mean for chronological age, or a decrease in height SD of more than 0.5 over 1 year in children over 2 years of age.
 - In the absence of short stature, a height velocity more than 2 SD below the mean over 1 year or more than 1.5 SD sustained over 2 years; this may occur in GHD, presenting in infancy, or in organic acquired GHD.
 - Signs indicative of an intracranial lesion.
 - Signs of multiple pituitary hormone deficiency (MPHD).
 - Neonatal symptoms and signs of GHD.
2. **Evaluation for genetic disorders:** Due to the advances in genetic testing, there has been an increase in the diagnosis of genetic disorders of GHD and MPHD. Children with following features should be considered for genetic testing:
 - Familial forms of isolated GHD or specific syndromic forms of multiple pituitary hormone deficiencies (genes PROP1 and POU1F1): these mutations may present with the following:
 - ◇ Early onset of growth failure.

- ◇ Positive family history and possible consanguinity.
 - ◇ Height more than 3 SD below the mean.
 - ◇ Extremely low GH response to provocation tests, including GHRH, and very low IGF-I and IGFBP-3 levels.
- Severe short stature (< -3 standard deviation score [SDS] for the population or > 3 SD lower than midparental target height).
 - Body disproportion and/or skeletal dysplasia.
 - Small for gestational age (SGA), who did not present adequate catch-up growth.
3. **Radiological evaluation:** Bone age should be documented in every child being investigated for GHD. There are several methods of bone age estimation (discussed in the previous chapters).

MRI (preferably) or CT of the brain is recommended when suspecting any intracranial pathology (tumors, septo-optic dysplasia). MRI features of pituitary (listed below) to be evaluated in cases of isolated GHD or MPHD are as follows:

- Pituitary height.
 - Pituitary volume.
 - Anatomy of the stalk.
 - Position of the posterior pituitary.
4. **Biochemical assessment of GHD:**
 - Assay considerations: At present, there is a wide range of assays available to measure GH, IGF-I, and IGFBP-3. Single measurement of GH is of no value because pulsatile secretion of GH and IGF-system peptides are stable during the day (serum half-lives of 12 to 16 hours).

The recommended GH reference preparation is a somatropin standard, IRP IS 98/574, 22k rhGH isoform. Immunometric and liquid chromatography/tandem mass spectroscopy

techniques are used in assays. Gender, age, and puberty-specific reference ranges of IGF-1 should be used, as different commercial assays give different values.¹⁵

- **Provocative tests:** Due to the pulsatile release of GH, standardized protocols are used for diagnosing GHD. The tests can be done with any of the following agents: arginine, clonidine, glucagon, insulin, and l-dopa, following overnight fasting. The diagnosis should be supported by two stimulations tests. A peak GH concentration below 7 mg/L supports the diagnosis of GHD. Clinical, auxological, radiological, and biochemical parameters should be taken into account when making a diagnosis.
- **Clonidine:** Clonidine stimulates GH by way of several mechanisms, including the stimulation of GHRH. It is administered orally at a dose of 5 mcg/kg (maximum 250 mcg orally), and peak GH secretion is expected at about 1 hour and serial GH levels are measured at 0, 30, 60, 90, and 120 minutes. Clonidine may cause modest hypotension and hypoglycemia, so patients should be monitored for these problems during the test. Estimates of this test's sensitivity and specificity vary considerably.
- **Arginine:** An IV infusion of 0.5 g/kg body weight (to a maximum of 30 g) is given over 30 minutes, and serial GH levels are measured at 0, 30, 60, 90, and 120 minutes. The maximum GH peak is expected at about 60 minutes. There are no side effects from this test, but overdoses have been described.
- **Glucagon:** Administration of glucagon causes transient hyperglycemia which, in turn, stimulates endogenous insulin secretion, followed by controlled hypoglycemia and consequent GH secretion. It is less risky than insulin-induced hypoglycemia (described below) and is a good choice for infants and young children. Glucagon is administered subcutaneously at a dose of 15 µg per kg (max 1 mg), and serum samples are drawn at 0 min, 30 min, 60 min, 90 min, 120 min, 180 min after the stimulus. Peak GH secretion occurs between 2 and 3 hours after glucagon administration; side effects are mild and transient, including nausea, vomiting, sweating, or headaches.
- **Insulin tolerance test:** Insulin-induced hypoglycemia is a potent stimulant of GH release, and it is therefore among the most specific tests for GHD. However, this test is less commonly used in children because of safety concerns. Insulin is administered intravenously at a dose of 0.10 (0.05–0.15 unit) unit per kg, and serum samples are drawn at 0 min and at hypoglycemia, (which commonly occurs within 15 minutes) to regular intervals of 30 min till 2 hours poststimulus.
- **New diagnostic test:**³⁰ Macimorelin, a ghrelin agonist that stimulates growth hormone secretion from pituitary, has recently been approved for adults. It has advantages of oral administration, fewer side effects, high sensitivity and specificity, but there are no published data of its use in children.
- It is important to remember that **before doing provocative tests**, it is important to make sure that child is **thyroid-sufficient and cortisol-sufficient**.
- Sex steroid priming is recommended prior to provocative GH testing in prepubertal boys older than 11 and in prepubertal girls older than 10 years. Depo testosterone 50 to 100 mg 1 week before the test, β-estradiol single dose 2 mg (wt > 20 kg), and 1 mg (wt < 20 kg) for 2 consecutive days before the test should be given to boys and girls respectively. This is done to prevent over diagnosis and treatment with growth hormone in children with CDGP.

- Conditions not requiring GH testing for diagnosis of GHD.
1. A diagnosis of GHD without GH provocative test fulfilling all three criteria:
 - Auxological criteria.
 - Hypothalamic-pituitary defect (such as major congenital malformation [ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk], tumor, or irradiation).
 - Deficiency of at least one additional pituitary hormone.
 2. GHD secondary to congenital hypopituitarism.
 - If a neonate with hypoglycemia fails to attain a serum GH value above 5 µg/L.
 - Has coexisting deficiency of at least one additional pituitary hormone.
 - The classical imaging triad (ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk).

Note: It is recommended to do two different stimulation tests to label a child as GHD before initiating treatment.

In a neonate with a high pretest probability of GHD, a random GH level < 7 ng/mL in the first week of life supports the diagnosis, and GH simulation test is considered unnecessary.

Growth Hormone Therapy^{15,30}

1. **Dose:** The Food and Drug Administration (FDA)-approved GH dose is 0.16 to 0.24 mg/kg/week (22–35 µg/kg/day), with subsequent titration to each patient. The IGF-1 levels are to be kept between 1 to 2 SD of the age and gender-matched references; higher values warrant a reduction in the dose of GH.
 2. **When to stop:** GH treatment at pediatric doses should be stopped.
 - If the growth velocity is below 2 to 2.5 cm/year.
 - Attained bone age of 14 in girls and bone age of 16 in boys.
 - Attained the target height.
3. **Safety issues:**
 - At every follow-up clinic visit, patient should be assessed for any signs or symptoms of intracranial hypertension, slipped capital femoral epiphysis, and scoliosis progression. A thorough physical examination should be done at every follow-up. It is advisable to screen for scoliosis prior to start of treatment.
 - In cases with MPPHD, the adrenal and thyroid functions should be reevaluated after initiation of GH. In some cases, which are already on hydrocortisone and/or levothyroxine, treatment may require increase in dosage.
 - Monitoring of glucose metabolism is required in GH recipients who are at increased risk of hyperglycemia due to insulin resistance.
 - For GH initiation in children surviving cancer, the treatment should only be started 1 year after successful completion of treatment (detailed explanation in chapter: endocrine disorders in cancer survivors).
 - It is recommended to provide information in cases of GHD with associated conditions and intrinsic increased risk of malignancy (e.g., neurofibromatosis-1, Down syndrome, Bloom syndrome, Fanconi anaemia, Noonan syndrome, and Diamond–Blackfan anemia), and about the lack of evidence concerning GH effect on malignancy risk in these groups.
 4. **Transitional care after childhood GH treatment:**
 - Persistent GHD is defined in conditions in:
 - ◇ Patients with multiple (≥ 3) pituitary hormone deficiencies (regardless of aetiology), or
 - ◇ GHD with a documented causal genetic mutation, or

- ◇ Specific pituitary/hypothalamic structural defect except ectopic posterior pituitary.
- Retesting of somatotrophic axis needed in:
 - ◇ Isolated GHD.
 - ◇ With only one additional pituitary hormone deficiency.
 - ◇ With MRI findings of small pituitary/ectopic posterior pituitary.
 - ◇ Postirradiation.

Note: Retesting should be done after withholding GH for 1 month.

- IGF-I concentration should be done first while evaluating for persistent GHD, and if found low, one should proceed to provocative testing.
- Cases diagnosed as persistent GHD should be started on GH treatment. However, there are no clear-cut guidelines on the time and dose of initiating treatment.

5. **Emerging treatment:**

- Long-acting growth hormone: Several pharmaceuticals companies are developing long-acting GH, which can be administered once weekly or less frequently and may be beneficial in improving adherence to the treatment.
- Oral ghrelin analogues: It may have potential to treat children with hypothalamic GH deficiency but may not be useful in severe pituitary GH deficiency.

■ Growth Hormone Resistance/Growth Hormone Insensitivity

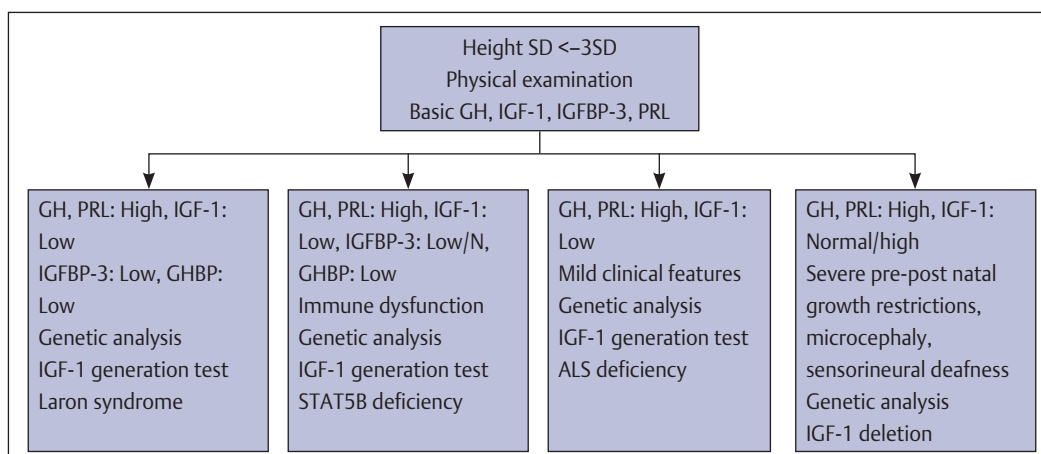
GH resistance occurs due to pathology, resulting in complete or partial interrupted activity of growth hormone, which can be genetic (primary) and acquired (secondary). GH insensitivity comprises a large spectrum of clinical manifestations. There are lots of phenotypical similarities with GH deficiency; however, high

levels of circulating GH are usually found. The most severe clinical form of GH insensitivity is Laron syndrome.^{31–36}

Clinical features of Laron syndrome are extreme short stature and retarded skeletal maturation. They may also have progressive obesity in early childhood, which is usually associated with high-body fat. The severities of craniofacial changes depend upon intensity of resistance and mainly reflect the underdeveloped facial bones.

Classification of Growth Hormone Resistance

1. Primary GH insensitivity (hereditary/congenital defects):
 - Bioinactive GH: It was first described in 1978 as mutant GH having reduced binding with GH receptor. In some cases, functional defects of GH-1 have been described. There is good response to human GH therapy.
 - Laron syndrome: Several GH receptor mutations have been described as being associated with high GH concentrations and low IGF-1 concentrations along with typical features (growth failure (untreated adult height -5 SD), frontal bossing, midface hypoplasia, and normal intelligence). A low concentration of growth hormone binding protein is consistent with diagnosis; however, it does not exclude the same.^{34–37}
 - STAT5B deficiency: It is a major component of signal transduction following activation of GH receptor. Mutated or absent protein leads to a similar clinical picture as Laron syndrome.³³
 - Acid labile subunit (ALS) deficiency: It is probably due to the loss of hepatic derived circulating IGF-1 which leads to less severe growth impairment as compared to Laron syndrome.^{38,39}
 - IGF-1 deletion and bioinactive IGF-1: Severe pre- and postnatal growth restrictions, microcephaly,



Flowchart 1.2 Algorithm for diagnosis of growth hormone insensitivity. Abbreviations: ALS, acid labile subunit; GHBP, growth hormone-binding protein; GH, growth hormone; IGFBP-3; insulin-like growth factor binding protein-3; IGF-1, insulin-like growth factor-1; N, normal; PRL, prolactin; SD, standard deviation; STAT5b, signal transducer and activator of transcription 5b.

sensorineural deafness, and developmental delay can be seen in such patients (Flowchart 1.2).³⁴⁻³⁷

2. **Secondary GH resistance (insensitivity) disorders:** It mainly includes acquired conditions, which may be partial or occasionally transient. These conditions include antibodies against GH or GH receptor and insensitivity secondary to malnutrition, liver disease, inflammatory bowel disease, poorly controlled diabetes, severe diseases and catabolic states.

Diagnosis

High initial levels of GH along with low IGF-1 levels and poor response to IGF-1 generation test can make a diagnosis of GH resistance. Following points are helpful in making a diagnosis.⁴⁰⁻⁴²

1. Auxological criteria (height SDS < -3 SD) and low IGF-I concentration.
2. Secondary IGF-1 deficiency (undernutrition, hepatic disease, etc.) to be excluded.
3. GH-binding protein (GHBP): A low level provides evidence in favor of diagnosis of Laron syndrome; however, normal level does not exclude it.

Table 1.4 Scoring system for GH insensitivity

Parameter	Criterion	Score
Height	< - 3 SD	1
Basal GH	> 2.5 ng/mL	1
Basal IGF-1	< 50 ng/mL	1
Basal IGFBP-3	< - 2 SD	1
IGF-1 generation test	Poor increase in IGF-1 (< 15 ng/mL) and IGFBP-3 (< 400 ng/mL)	1
GH binding %	10%	1

Abbreviations: IGFBP-3, insulin-like growth factor binding protein-3; IGF-1, insulin-like growth factor-1; GH, growth hormone.

4. IGF-1 generation test: There are various protocols for IGF-1 generation test. Basal IGF I and IGFBP 3 samples are taken on day 1 and GH is administered in doses of 0.1 unit/kg for 3 days, and on the 4th day again, IGF1 and IGFBP3 samples are taken. Normal response is considered with a rise of IGF I by > 15 ng/mL and IGFBP3 by > 400 ng/mL.

A scoring system for GH resistance is also advised. A total score of > 5 is supportive of Laron syndrome (Table 1.4).

Genetic Studies

Genetic studies along with phenotypical and biochemical evidence are confirmatory for diagnosis of GH insensitivity. Laron syndrome is mainly due to the mutation in GH receptor and its coding region.

Treatment

Recombinant human IGF-I therapy is recommended for the treatment of primary IGF-I deficiency in children meeting the following criteria:⁴³

- Height SDS < - 3 SD.
- IGF-I concentrations < 2.5th centile for age and gender.
- GH sufficiency.
- Exclusion of secondary forms of IGF-1 deficiency such as malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

The starting dose is 40 mg/kg twice daily, which is increased over approximately 3 months to the therapeutic dose of 120 mg/kg twice daily. The main complication associated with IGF-1 treatment is hypoglycemia; therefore, it should be administered with meals. It is advisable to admit the patient during initial days of IGF-1 treatment to monitor for hypoglycemia. Contraindications of IGF-1 therapy are active malignancy and acute allergic reaction. Other side effects are intracranial hypertension, slipped capital femoral epiphyses, local and systemic allergic reactions and lipohypertrophy. IGF-1 antibodies can develop, which leads to decreased treatment efficacy.

Note: During the course of treatment, if the child develops poor response to treatment, then the secondary causes (malnutrition and hypothyroidism) should be reevaluated.

Other Causes of Short Stature

There are several conditions associated with growth altering in children, resulting in short

stature where there isn't a deficiency of GH; in these conditions, there is some amount of GH resistance and other contributory factors impeding growth.

The commonly seen conditions discussed below are Turner syndrome (TS), SGA, Silver-Russell syndrome, Noonan syndrome, Prader-Willi syndrome, idiopathic short stature.

Turner Syndrome

TS is one of the most common chromosomal anomalies in girls. It affects 25 to 50 per 100,000 females, irrespective of ethnic background.⁴⁴ TS (or Ullrich-Turner syndrome) may be defined as the combination of characteristic physical features and complete or partial absence of the second sex chromosome, with or without cell line mosaicism.

Etiology

TS has several genotypes and almost 50% of girls have the 45,X karyotype. The other common mosaic abnormalities are 45,X/46,XX (15–25%), 45,X/47,XXX; 45,X/46,XX/47,XXX (3%). Structural abnormality of the X chromosome is seen as ring chromosome X, isochromosome of the long arm [i(X)q], or a partial deletion of the short arm (delXp). About 12% cases can be 45,X/46,XY and the Y chromosome can cause gonadoblastoma in future and may require preventive gonadectomy. In TS with XY karyotype, occurrence of gonadoblastoma should always be kept in mind.^{45–47}

Clinical Presentation

TS has a wide variety of clinical presentation with different clinical features from neonatal period to adult.^{45–48}

Presentation during Neonatal Period

1. Features associated with lymphedema: Swollen hands and feet, webbing of neck.
2. Dysplastic or hypoplastic nails: Along with lymphedema, fingers and toes have characteristic sausage-like appearance.
3. Congenital dislocation of hip.

Associated Features

1. High-arched palate, dental overcrowding, malocclusion, micrognathia, retrognathia.
2. Excessive numbers of nevi.
3. Increased carrying angle: Cubitus valgus.
4. Madelung deformity of wrist.
5. Short fourth and fifth metacarpals and metatarsals.
6. Shield chest: Broad chest with widely spaced nipples.
7. Low posterior hairline.

Presentation during Childhood Period

1. Short stature.
2. Cardiac defects: Left-sided obstructive defects predominate, especially bicuspid aortic valve (BAV; 30–50%) and coarctation of the aorta (COA) (30%).
3. Hypertension: May be due to COA, but it can occur in absence of cardiac defects also.
4. Obesity: Girls with TS have tendency to gain weight. Due to their characteristic features such as shield chest, stocky built, and short stature, the appearance may be exaggerated.
5. Eyes: Epicanthus and near sightedness, ptosis, strabismus, amblyopia, and cataracts.
6. Ears: Involve outer, middle, and inner ear. Outer ear: mild malformation of outer ear; middle ear: serous otitis media; inner ear: sensorineural deafness.
7. Speech delay.
8. Thyroid: Hypothyroidism due to thyroiditis and hypothyreosis seen in 10 to 30% of girls with TS.
9. Neurocognitive and psychosocial problems: Deficits in visual-spatial/perceptual abilities, nonverbal learning disorder, motor function, emotional immaturity, attention, and social skills.

Presentation during Adolescent Period

1. Delayed puberty: Adrenarche occurs at an age same as in general population. TS with ovarian failure have absent breast development and amenorrhea (primary or secondary).
2. Scoliosis: Further contribute to short stature.
3. Gastrointestinal (GI) bleeding: Due to intestinal vascular malformations.

Diagnosis and Genetics

Testing for TS should be considered in a female with typical signs. Standard 20-cell karyotype is usually recommended in girls with suspected phenotype; additional metaphases may be counted, or fluorescence in situ hybridization (FISH) studies performed if initial test karyotypic negative in strongly suspected cases.⁴⁸

Indications for Karyotyping⁴⁸

1. As the only clinical feature:
 - Fetal cystic hygroma, or hydrops, especially when severe idiopathic short stature.
 - Obstructive left-sided congenital heart defect.
 - Unexplained delayed puberty/menarche.
 - Couple with infertility.
 - Characteristic facial features in a female.
2. At least two of the following:
 - Renal anomaly (horseshoe, absence, or hypoplasia).
 - Madelung deformity.
 - Neuropsychologic problems and/or psychiatric issues.
 - Multiple typical or melanocytic nevi.
 - Dysplastic or hyperconvex nails.
 - Other congenital heart defects.
 - Hearing impairment < 40 years of age together with short stature.

Prenatal Diagnosis

Chorionic villous sampling or amniocentesis can detect sex chromosome anomalies prenatally, regardless of the indication. Antenatal ultrasonography can suggest indicative features such as increased nuchal translucency, frank cystic hygroma, coarctation of the aorta, left-sided cardiac defects (which should be further imaged by fetal echocardiography), brachycephaly, renal anomalies, polyhydramnios, oligohydramnios, and growth retardation. However, all these features are only indicative of TS; for confirmation, chorionic villous sampling or amniocentesis is required. Chromosome analysis should be repeated in all patients postnatally, as amniocentesis karyotype reflects fibroblast analysis.⁴⁸

Management

TS has a wide variety of clinical presentation and requires a multidisciplinary approach.⁴⁸

- **Growth and puberty:** TS girls should always be plotted and monitored on Turner specific growth chart (available from CDC) (no country/ethnicity specific charts are available).
 - ◇ Growth hormone is the mainstay of growth promoting therapy in TS.
 - ◇ Growth hormone should be initiated early (around 4–6 years of age) in cases of height velocity below 50th percentile for a period of 6 months.
 - ◇ GH should be initiated at doses of 45 to 50 $\mu\text{g}/\text{kg}/\text{day}$ or 1.3 to 1.5 $\text{mg}/\text{m}^2/\text{day}$ (4.0–4.5 $\text{IU}/\text{m}^2/\text{day}$) in most instances, increasing to 68 $\mu\text{g}/\text{kg}/\text{day}$ (2.0 $\text{mg}/\text{m}^2/\text{day}$) if adult height potential is substantially compromised. It should be further monitored with height measurement every 4 to 6 months along with annual IGF-1 monitoring. IGF-1 levels may be needed above 2 SD for effective growth, but this decision should be taken with informed consent of parents. IGF-1 above 3 SD requires dose reduction.
 - ◇ There have been few observational studies suggesting increased risk of

intracranial hypertension, slipped capital femoral epiphysis, especially development or progression of scoliosis, and impaired carbohydrate metabolism among TS receiving GH in comparison to general population.

- ◇ In cases of delay in diagnosis or initiation of GH, concomitant treatment with oxandrolone from the age of 10 years or older at 0.03 $\text{mg}/\text{kg}/\text{day}$ and maintained below 0.05 $\text{mg}/\text{kg}/\text{day}$ has been advised; however it's not available in India.
- ◇ Low-dose estrogen replacement should be started between 11 and 12 years of age, which to be gradually increased to adult dose over 2 to 3 years of period. Progesterone should be added once breakthrough bleeding occurs or after 2 years of estrogen treatment. **Noteworthy** point here is if the girl is extremely short, it can be delayed upto 14 years).
- **Cardiovascular issues:** Transthoracic echocardiography (TTE) is recommended at the time of diagnosis, as there are high chances of associated cardiovascular defects. Cardiac MRI should be undertaken soon, as it is feasible without general anesthesia. Cardiac MRI or TTE is recommended every 5 years for monitoring.
- **Fertility:** Young mosaic TS with persistent ovarian function should be counseled about fertility and oocyte preservation. Pregnancy should be monitored closely in view of increased cardiovascular risks. Spontaneous pregnancy occurs in 4.8–7.6% and pregnancy with oocyte donation occurs in 16–40% of turner patients. Different art is now available for turner patients with variable results.
- **Comorbidities:**
 - ◇ Ear: audiometric evaluation every 5 years and aggressive treatment of middle ear diseases.
 - ◇ Screening for hypothyroidism (FT4, TSH) every year.

- ◇ Annual measurement of HbA1c.
- ◇ Annual measurement of lipid profile in patients with at least one cardiovascular risk from 18 years of age.
- ◇ Ophthalmic evaluation at diagnosis and correction of refractive error at diagnosis or after 18 months of age.
- ◇ 6-monthly clinical evaluations for scoliosis during GH treatment.
- ◇ Screening for vitamin D deficiency from 9 to 11 years of age and every 2 to 3 years thereafter.
- ◇ Dual energy X-ray absorptiometry (DEXA) scans to monitor bone mineral density after hormone replacement therapy has been started.

Small for Gestational Age (SGA)

SGA is defined as birth weight or length < -2 SD below mean. Incidence of SGA is around 27% for birth weight < -2 SD in India. Ninety percent of these children will experience catch-up growth by 2 years of age; however, children born prematurely may continue to catch up by 4 years of age.⁴⁹

In the neonatal period, SGA is prone to hypoglycemia, hypotension, and necrotizing enterocolitis. These children can have lower cognitive performance in later childhood and have increased risk of hypertension, type 2 diabetes, hyperlipidemia, and cardiovascular disease in adult life. Rapid weight gain in first 6 months of life is associated with increased cardiovascular and metabolic risk in adult life.

Management

GH is recommended in SGA children with failed catch-up growth till 4 years of age. The European Society of Pediatric Endocrinology recommends GH treatment in children of age > 4 years, birth weight < -2 SDS, height SDS < -2.5 SD compared with population reference data and more than 1 SD below MPH SDS and growth velocity SDS < 0 SD. GH should be initiated with doses of 35 (EMEA-2003 guidelines) to 70 (US-FDA-2007 guidelines) mcg/kg/day, keeping the IGF-1 below 2 SD for the reference

population. IGF-1 levels may be needed above 2 SD for effective growth, but this decision should be taken with informed consent of parents. None of the studies shows any treatment related safety issues associated with higher levels of IGF-1, however, long term data is lacking. GH should be continued till growth velocity is less than 2 cm/year. US-FDA has approved GH in SGA in any child who has not catch up growth till 2 years of age.^{30,50}

SGA children are more prone to have early puberty, which may require LHRH analogue treatment. Thyroid function test should be measured before initiation of treatment. IGF-1 is monitored initially and on follow-up for titration of GH doses.

Silver–Russell Syndrome (SRS)

SRS is a rare syndrome with global incidence of 1:30,000 to 1:100,000. The etiology of SRS is extremely heterogeneous, and its underlying molecular cause can be identified in approximately 60% of clinical diagnosed SRS. The most common identifiable causes are loss of methylation on 11p15 and uniparental disomy of chromosome 7.

SRS is a clinical diagnosis and negative molecular results do not exclude the diagnosis. Clinical scoring is based on the Netchine–Harbison clinical scoring system. It is diagnosed by a scores at least 4 out of 6 of the clinical signs listed in **Table 1.5**.⁵¹

An alternative syndromic diagnosis should be considered in cases with negative molecular diagnosis and positive history of consanguinity or family history of growth failure or patients with atypical features.

Management⁵¹

- Feeding difficulties are common, which may require appetite stimulant and active management of gastroesophageal reflux.
- Urinary ketones may be monitored in children with hypoglycemia during illness to be alert for requirement of active hospital-based management

Table 1.5 Netchine–Harbison clinical scoring system

Criteria	Findings
SGA (birth weight and/or birth length)	≤ 2 SDS for gestational age
Postnatal growth failure	Height at 24 ± 1 months ≤ 2 SDS or height ≤ 2 SDS below mid-parental target height
Relative macrocephaly at birth	Head circumference at birth ≥ 1.5 SDS above birth weight and/or length SDS
Protruding forehead	Forehead projecting beyond the facial plane on a side view as a toddler (1–3 years)
Body asymmetry	Limb length discrepancy of ≥ 0.5 cm or arm asymmetry or limb length discrepancy < 0.5 cm with at least two other asymmetrical body parts (one nonface)
Feeding difficulties	Current use of a feeding tube or cyproheptadine for appetite stimulation
Low BMI	BMI ≤ 2 SDS at 24 months

Abbreviations: BMI, body mass index; SDS, standard deviation score; SGA, small for gestational age.

- During treatment of hypoglycemia or during fasting for any surgery, 10% dextrose should be used. Glucagon is not useful in cases of hypoglycemia due to poor glycogen reserve.
- GH stimulation test should be avoided. GH therapy should not be started until calorie deficits are addressed. GH therapy should be initiated from 2 to 4 years of age with a dose of 35 mcg/kg/day. IGF-1 and IGFBP-3 monitoring should be done at least once a year.
- GH therapy should be stopped at bone age of 14 year in girls and 16 years in boys or if increase in height is < 2 cm/year over a period of 6 months.
- Early puberty is common in these patients, which may require LHRH agonist treatment in cases of true central precocious puberty. Its decision should be taken on an individual case basis.
- Rapid weight gain should be avoided, and one should be advised about future risks associated with it such as insulin resistance, polycystic ovarian syndrome, etc.

Noonan Syndrome (NS)

NS is an autosomal dominant disorder with a prevalence of 1:1000 to 1:2500. The most

common mutations associated are PTPN11 (~50% cases), SOS1 (~10%), RAF1 (~10%), KRAS (< 2%), and NRAS (<1%).⁵²

Clinical diagnosis is based on the criteria mentioned in **Table 1.6**.⁵³

Clinical diagnosis is considered in cases with typical facial features along with one major and two minor criteria other than facial feature or suggestive facies along with two major and three minor criteria other than facial feature.

Management^{54,55}

- Full cardiac assessment is indicated at the time of diagnosis as congenital heart defects (e.g., pulmonary stenosis, hypertrophic cardiomyopathy, and atrial septal defect) are commonly associated. If a cardiac anomaly is identified, further follow-up is required.
- Formal developmental and neuropsychological assessment is advised after 6 months of age or at diagnosis. Developmental assessment every year from 5 to 18 years of age.
- Renal ultrasound at the time of diagnosis.
- Coagulation profile (prothrombin time [PT], activated partial thromboplastin time [APTT]) at 5 years of age or earlier if any surgery is planned.

Table 1.6 Clinical diagnostic criteria for Noonan syndrome

	Features	Major	Minor
1	Facial	<p>Typical</p> <p>Newborn: Tall forehead, low posterior hairline, hypertelorism, downslanting palpebral fissures, epicanthal folds, short and broad nose, depressed root of nose, upturned tip, deeply grooved philtrum, high wide peaks of the vermilion, micrognathia, excessive nuchal skin</p> <p>Infancy: Large head, tall and prominent forehead, hypertelorism, ptosis, or thick-hooded eyelids, short and wide nose, depressed nasal root</p> <p>Adolescence: Myopathic facies, nasal bridge is high and thin, webbing of neck</p> <p>Others: Blue green irises, arched and diamond-shaped eyebrows, low-set, posteriorly rotated, thick helices</p>	Suggestive face
2	Cardiac	Pulmonary valve stenosis and/or HCM	Other cardiac defects
3	Height	< 3rd centile	< 10th centile
4	Chest wall	Pectus carinatum/excavatum	Broad thorax
5	Family history	First-degree relative with definite Noonan syndrome	First degree relative suggestive of Noonan syndrome
6	Other	Mild developmental delay, cryptorchidism and lymphatic dysplasia	Mild developmental delay, cryptorchidism, or lymphatic dysplasia

Abbreviation: HCM, hypertrophic cardiomyopathy.

- Ophthalmology assessment at the time of diagnosis as visual problems (e.g., posterior segment ocular changes and anterior segment ocular abnormalities) is common. Repeat assessment every 2 years or sooner, if required.
 - Cryptorchidism is commonly associated and should be treated in standard way at appropriate time.
 - Hearing assessment is advised after 6 months of age or at time of diagnosis, whichever is later.
 - Height and weight should be plotted on Noonan specific growth chart (available from CDC) for at least 3 times a year till 3 years of age and then annually thereafter.
 - Full dental assessment between age of 1 to 2 years and then annually.
 - GH is licensed in USA and Japan for use in NS; however, it should be used with great caution in patients with cardiomyopathy. GH testing is not indicated; it can be started in children with < -2.5 SD below the mean on population specific standard charts. Half of children with NS can grow normally without GH treatment.
 - Patient on GH should have periodic assessment for scoliosis.
- Note: GH therapy in cases with RAF-1 mutation is controversial due to progressive ventricular hypertrophy. Hence, if initiated, they should be closely monitored for current cardiac conditions and any progression.

Prader–Willi Syndrome (PWS)

PWS is a complex congenital disorder caused by lack of expression of paternally inherited genes on chromosome 15q11–q13, which may be due to deletion of parental allele (75%) or duplication

of maternal allele or imprinting abnormalities. It is characterized by typical facial features (thin upper lip and almond shaped eyes), obesity, hyperphagia, hypogonadism, developmental delay, and learning difficulties. During neonatal period, hypotonia and feeding difficulties are also common.^{56,57} Genetic testing is required to confirm the diagnosis.⁵⁸

Management

Management of PWS include the following:

- During neonatal period, nasogastric feeding might be required due to hypotonia and poor sucking.
- Developmental assessment should be undertaken and active physiotherapy along with language and behavior therapy is helpful in PWS.
- GH deficiency is seen in PWS and recent studies advocate earlier initiation of GH due to better psychomotor development. Most patients develop short stature early in life. GH testing before initiation is not mandatory. GH is initiated with dose of 9 to 12 mcg/kg/day and can be increased to 35 mcg/kg/day. IGF-1 should be assessed periodically to keep in between range of +1 to +2 SDS during childhood.
- Obesity and hyperphagia are common and may require active intervention such as low-calorie diet and exercise. GH has a positive impact on body composition and tone.
- Scoliosis and obstructive sleep apnea syndrome (OSAS) are common in patients with PWS and potential side effects during treatment with GH and should be actively looked for during follow-up visits. OSAS can worsen after starting of GH therapy.
- GH should not be started in patients with severe obesity, uncontrolled diabetes, untreated severe OSAS, active cancer, and active psychosis.

Idiopathic Short Stature (ISS)

ISS is defined as height < -2.25 SD below mean for age and sex-specific reference population. Familial short stature and CDGP along with other causes of short stature should be ruled out before considering diagnosis of ISS.⁹

A thorough physical examination looking for subtle dysmorphism, disproportion, and phenotypic features of other causes of short stature including skeletal dysplasia should be undertaken. Laboratory evaluation should include CBC, kidney function test (KFT), LFT, IgATtG, karyotype (for female), bone age, TSH, free T4, and IGF-I. IGF-1 can be low in 50% cases with ISS along with normal GH stimulation. GH testing is required in cases with decreased IGF-1 to rule out GH deficiency. Several monogenic causes are being identified among cohorts labeled as ISS previously. There may be further identification of genetic causes in this group in future.

The US FDA had approved use of GH (0.3–0.37 mg/kg/week [42.8–52.8 mcg/kg/day]) in ISS with height < -2.25 SD below mean. Periodic assessment of IGF-1 along with monitoring for other side effects of growth hormone is recommended.^{9,30,50}

It is important to note that ISS has a very variable response to GH, due to which prediction models cannot be applied in ISS. It is not an approved indication in many countries yet.

Other options of treatment in cases of ISS are LHRH agonist and aromatase inhibitor. LHRH agonist has a modest outcome, while aromatase inhibitor has a good outcome on short-term follow up. However, neither of these is approved at present for treatment.

Tall Stature

Introduction

Tall stature is defined as a height ranging beyond the threshold of +2 SD of the average population size for the age and gender or > 2 SDS of target height.⁵⁸

Etiology

Intrauterine/infantile overgrowth:

- Infant of diabetic mother: Increased maternal glucose concentration can lead to increase in fetal glucose and subsequent hyperinsulinemia and increased growth.
- Cerebral gigantism (Sotos syndrome): Autosomal dominant condition due to deletion of NSD1 gene (chromosome 5).
- Beckwith–Wiedemann syndrome: Genetic imprinting disorder involving chromosome 11p.

Childhood/adolescent overgrowth

1. Endocrine disorders:
 - GH excess (acromegaly/gigantism): Increased secretion of GH.
 - Precocious puberty (central or peripheral): It is not an actual overgrowth, as final height may be less or same as actual height, and early sex steroid exposure will lead to early epiphyseal fusion as well.
 - Hyperthyroidism: It is associated with increased bone age and symptoms such as tachycardia, palpitation, tremor, etc.
 - Testosterone/estrogen deficiency or receptor insensitivity: It will lead to continued growth due to lack of epiphyseal closure.
 - Aromatase deficiency: Aromatase enzymes are required for conversion of testosterone to estrogen, deficiency of which will lead to continued growth.
 - Cortisol resistance: Endogenous (elevated ACTH) or exogenous.
2. Nonendocrine disorders:
 - Simple obesity: Nutritional.
 - Fibrillin gene mutation: Marfan syndrome.
 - Deficiency of cystathionine synthase enzyme: Homocystinuria.

- Melanocortin 4 receptor (MC4R) mutation.
- Klinefelter syndrome (47XXY): Sex chromosome aneuploidy (one or more supplementary X chromosome).
- 47XYY: Aneuploidy of Y chromosome.
- Triple SHOX gene: Triple X syndrome.
- FMR1 CGG repeats: Fragile X syndrome.

Approach to Tall Stature

1. Plot on growth chart keeping in mind race, sex, and ethnicity to confirm the diagnosis.
2. Estimate the MPH to look for familial tall stature.
3. Look for pubertal staging, as early puberty may result in growth acceleration.
4. Timing of increased growth rate: Depending upon the various causes as described above, it is necessary to ascertain the timing of increased growth rate. As in cases such as Beckwith–Wiedemann in infant of diabetic mother, intrauterine growth acceleration will have increased growth at birth. If there is a sudden increase in growth velocity after infancy, conditions such as hyperthyroidism, growth hormone excess, obesity, and constitutional advancement of growth should be kept in mind.⁵⁹
5. Anthropometry:
 - Arm span > standing height: Marfan syndrome.
 - Macrocephaly: Sotos and Weaver syndromes.
 - BMI: Obesity–monogenic obesity.
6. Behavioural and developmental history: Sotos, triple X, fragile X, homocystinuria, etc.
7. Calculate predicted adult height by using Bailey–Pinneau, TW, or Bone-Xpert method with the help of bone age. They are not entirely reliable and might

underestimate the predicted height. If there are no syndromic features or features of growth, acceleration is present and predicted adult height is more than the MPH, and hypoestrogenism or estrogen resistance, causing delayed epiphyseal closure, should be considered.⁶⁰

Treatment

Treatment should only be considered after evaluation of hormonal causes, as it might need treatment of underlying condition. Epiphyseal fusion is required to stop the growth, which has been tried in the past for tall stature.⁶¹ For females, ethinyl estradiol is given in dose of 1 to 3 mg for short duration, as long-term use can cause decreased fertility or increase in risk of ovarian failure for up to 2 months (ethinyl estradiol is not easily available, instead estradiol valerate 2 mg can be used).^{62,63} For males, testosterone 250 mg is given intramuscularly (IM) every 2 weeks up to 4 to 6 months.⁶⁴

Growth Hormone (GH) Excess

It is a rare disorder. Gigantism is caused by excess of GH in a growing child (before epiphyseal fusion), while acromegaly is due to excess of GH after epiphyseal fusion. GH excess can be due to:^{65,66}

- Excess secretion from pituitary (pituitary adenoma or somatotroph hyperplasia).
- Excess release from hypothalamus (GHRH).
- Decrease in somatostatin inhibition.
- Ectopic source of GH or GHRH.

Various syndromes can also be associated with GH excess:

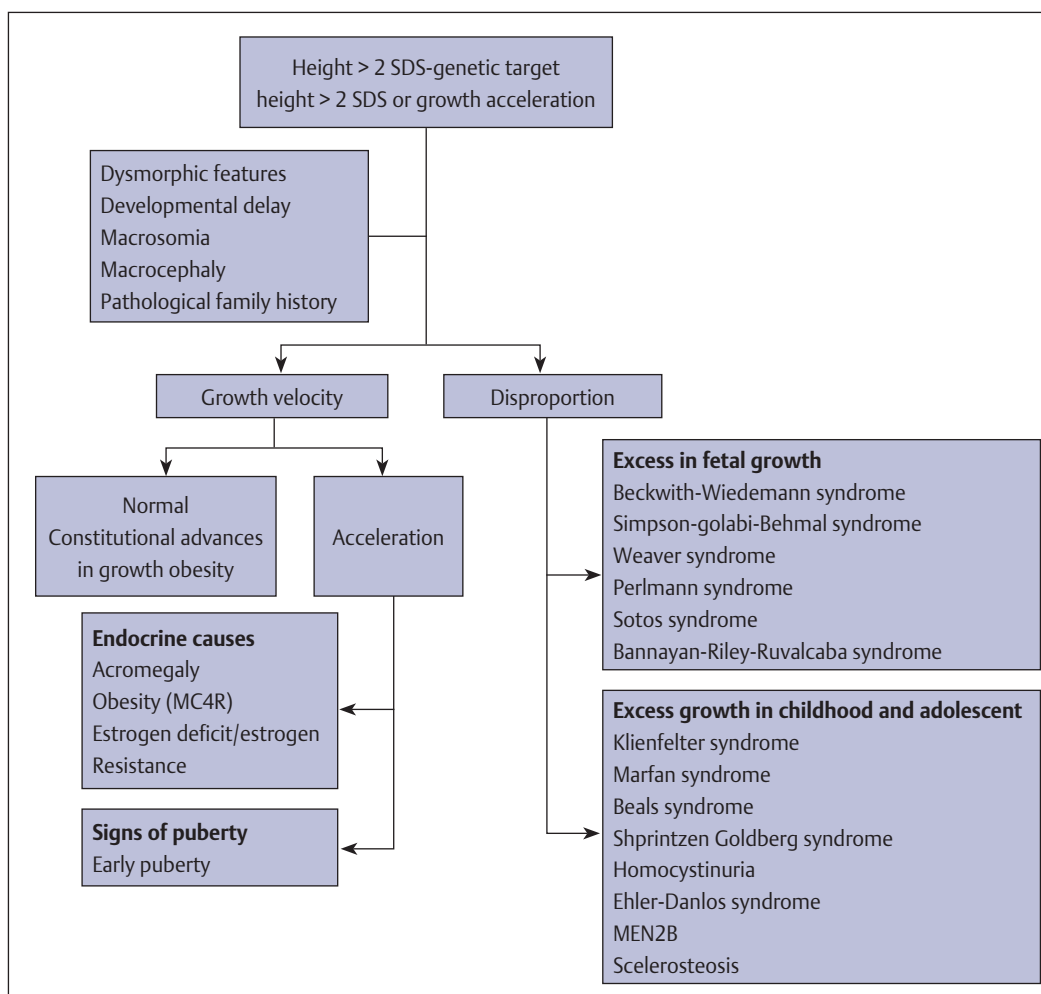
1. Multiple endocrine neoplasia type 1 (MEN 1): MENIN.
2. Multiple endocrine neoplasia type 4 (MEN 4): Cyclin-dependent kinase inhibitor (CDKN1B).
3. Familial isolated pituitary adenoma: Aryl hydrocarbon receptor-interacting protein (AIP).

4. McCune–Albright syndrome: GNAS1.
5. Carney complex: PPKAR1A.
6. X-linked acrogigantism (X-LAG): GPR101.
7. 3PA (paraganglioma, pheochromocytoma, and pituitary adenoma association): Succinate dehydrogenase (SDH A-D).

Diagnostic Evaluation^{65,66}

1. **IGF-1 level:** IGF 1 is a composite measure of basal GH secretion. It should be interpreted with regard to age and Tanner stage.
2. **Random GH level:** It is not reliable. GH secretion remains pulsatile in adenomatous pituitaries as well.
3. **Oral glucose challenge test:** It is the gold standard test for the diagnosis. It is based on the ability of glucose load to suppress GH. A basal GH sample is taken, following which a 1.75 gm/kg (maximum 75 gm) of oral glucose load is given; GH should suppress within 30 to 120 mins. A value of GH > 1 mcg/L is considered GH excess.
4. **Visual field testing:** It is required in cases of optic chiasma compression, and periodic monitoring is also required.
5. **Radiographic imaging:** Dynamic pituitary MRI (using pituitary MRI protocol to increase sensitivity) is recommended in cases of GH excess, which will help in determining tumor size, location, and invasiveness.
6. **Other investigations:** Other pituitary hormones also should be evaluated such as prolactin, 8am cortisol, and thyroid hormones. A sleep study must be undertaken if symptoms of snoring or daytime somnolence are present. HbA1c is required to rule out diabetes mellitus.

An echocardiogram is required, especially in older patients with GH excess, as there might be associated cardiac conditions such as valvular



Flowchart 1.3 Algorithmic approach for diagnosis of tall stature.

heart disease, hypertrophic cardiomyopathy, and endothelial dysfunction (**Flowchart 1.3**).

Treatment

Goals of treatment are as follows:

1. Remove or shrink the tumor.
2. Normalize GH secretion and IGF 1 levels.
3. Avoid or minimize long-term complications.

Surgery is the mainstay of therapy, while medical and/or radiation therapy are often needed as adjuvant.

1. **Medical treatment:** It is sometime used preoperatively to decrease the tumor size for better surgical outcomes or post-operatively for biochemical control.
 - Several types of somatostatin analogues are available:
 - ◇ Long-acting octreotide: 10 to 40 mg every 4 weeks and slowly titrated until IGF-1 is normal. It has greater affinity for somatostatin type (sst) 2 and sst5 receptors found in the pituitary gland,

pancreas, and a lesser affinity for sst1, sst3, and sst4.⁶⁷

- ◇ Lanreotide: Starting dose of 60 to 120 mg every 4 weeks, depending on IGF-1 level. It has similar affinity as long-acting octreotide.⁶⁸
 - ◇ Pasireotide: It is given in dose of 20 to 60 mg every 4 weeks. It binds to sst1–5, with high affinity for the sst1–3 subtypes and highest affinity for the sst5 subtype.¹¹
 - Pegvisomant is a GH receptor antagonist that blocks the peripheral production of IGF-1 in a dose-dependent manner.
2. **Surgical therapy:** Surgical resection is the treatment of choice in cases of surgically resectable tumors and those in close proximity to optic chiasma. GH will decrease immediately following surgery, while IGF-1 will normalize later due to differential half-life.⁶⁹
 3. **Radiation therapy:** In cases of residual tumor postsurgery, radiotherapy is required. Newer advances in radiotherapy have fewer complications such as stereotactic radiotherapy, photon therapy, or proton beam therapy.

These patients require long-term follow-up and care, as some of the patients may require multiple pituitary hormone replacement, which can be due to residual tumor compression or surgical and radiation treatment. Cardiac defects associated with GH excess may reverse with appropriate biochemical control. Insulin resistance is commonly associated with chronic GH excess, which can further worsen with pasireotide.

Key Points

1. Growth chart charting both height and weight and bone age are essential tools in any pediatric department.
2. The diagnosis of GHD remains a clinical one, where one incorporates the

auxologic, anatomic, and laboratory data to arrive at a diagnosis.

3. An MRI of the hypothalamus and pituitary gland should be performed in all patients diagnosed with GHD.
4. Genetic diagnosis has an important role in short stature for prognosticating the patient and caregivers by aiding the diagnostic odyssey.
5. Acquired GH resistance is relatively common complication of variety of chronic diseases and should be kept in mind.
6. TS should be looked for in any female presenting with short stature.
7. About 10% of SGA children do not catch up by the age of 2 to 4 years and require GH treatment.
8. PWS represents a clinical scenario in which there is clear documentation of benefit of GH therapy that extends far beyond height gain.
9. ISS should only be considered after a comprehensive evaluation and ruling out any organic etiology.
10. Growth hormone is approved in growth hormone deficient conditions (Isolated GHD, Panhypopituitarism, Praderwilli syndrome) and non growth hormone deficient conditions (Turner syndrome, Noonan syndrome, SHOX deficiency, SGA, Silver Russell syndrome and Idiopathic short stature, CKD).

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