INDIAN ACADEMY OF PEDIATRICS

IAP Specialty Series On

PEDIATRIC ENDOCRINOLOGY

SECOND EDITION

Editors
Dr. Nalini S Shah
Dr. Sudha Rao



IAP National Publication House, Gwalior
JAYPEE

CONTENTS

SECTION 1: GROWTH

Chapter 1: Approach to a Child with Short Stature **3**
Sudha Rao

- *Normal Growth Velocity 3*
- *Causes of Short Stature 4*
- *Evaluation of a Child with Short Stature 4*
- *Anthropometry 5*
- *Approach to Evaluation of Short Stature 7*

Chapter 2: Physiological Short Stature **10**
Preeti Dabadghao

- *Constitutional Delay in Growth and Puberty 10*
- *Familial Short Stature 11*

Chapter 3: Growth Hormone Deficiency **15**
Shaila Bhattacharyya

- *Growth Hormone Physiology 15*
- *Evaluation 17*

Chapter 4: Turner Syndrome **23**
Archana D Arya

- *Case Discussion, Evaluation and Management 23*

Chapter 5: Systemic Illness and Short Stature **31**
Rajesh R Joshi

SECTION 2: THYROID DISORDERS

Chapter 6: Hypothyroidism in Childhood and Adolescence **43**
Karnam Ravikumar

- *History 44*
- *On Examination 45*
- *Investigations 46*
- *Treatment 47*

Chapter 7: Hyperthyroidism **51**
VK Bhardwaj

- *When to Suspect and What to Ask for in History? 52*
- *What to Look for on Clinical Examination? 53*
- *What are the Investigations to Ask for? 54*
- *How to Treat? 55*

Chapter 8: Goiter **59**
Vaman Khadilkar

- *Presenting Complaint 59*
- *History 59*
- *Confirm Thyroid Swelling 60*
- *Grading of Goiter 60*
- *Euthyroid Goiter 62*

Chapter 9: Newborn Screening for Congenital Hypothyroidism **64**
Anju Virmani

- *Approach to Newborn Thyroid Screening 69*

SECTION 3: PUBERTAL DISORDERS

Chapter 10: Precocious Puberty **73**
Prisca Colaco

- *Normal Pubertal Progression 73*
- *Definition of Precocious Puberty 73*
- *Classification 73*
- *Evaluation 74*
- *Treatment 76*
- *Psychological Support 77*

Chapter 11: Delayed Puberty **81**
Anurag Bajpai

- *Criteria 81*
- *Confirmation 81*
- *Differential Diagnosis 81*
- *Important Causes 81*
- *Evaluation 82*
- *Examination 84*
- *Investigations 84*
- *Management 88*

Chapter 12: Pubertal Gynecomastia **91**
Kavitha Bhatt

SECTION 4: CALCIUM AND VITAMIN D DISORDERS

Chapter 13: Rickets: Diagnostic Approach and Management **99**
Anju Seth, Varun Aggarwal

- *Epidemiology of Rickets 99*
- *Etiology 99*
- *Approach and Management 105*

Chapter 14: Hypocalcemia in Infants and Children **114**
Abhishek Kulkarni, Vijayalakshmi Bhatia

- *Overview of Calcium Homeostasis 114*
- *Definition of Hypocalcemia 114*
- *Causes of Hypocalcemia 115*
- *Clinical Features 117*
- *Approach to a Case of Hypocalcemia 117*

- *Investigations 117*
- *Sample Collection and Report Interpretation 118*
- *Management of Hypocalcemia 120*

SECTION 5: OBESITY IN CHILDHOOD

Chapter 15: Obesity in Childhood **127**
Subrata Dey
- *Clinical Approach to Childhood Obesity 128*
- *Treatment 129*

SECTION 6: DISORDERS OF CARBOHYDRATE METABOLISM

Chapter 16: Type 1 Diabetes Mellitus in Children and Adolescents **137**
Aspi J Irani
- *Confirming the Diagnosis of Diabetes Mellitus 138*
- *Defining the Type of Diabetes 138*
- *Looking for Co-morbidities at Presentation 139*
- *Broad Principles and Goals of Management 139*
- *Selecting the Appropriate Insulin Preparations, Regimen and Dosage 140*
- *Principles of Meal Planning 141*
- *Planning Physical Activity 142*
- *Home Monitoring 143*
- *Clinic Monitoring 143*
- *Hypoglycemia 144*
- *Sick Day Management 145*
- *Ensuring Patient Compliance with the Treatment Regimen 145*

Chapter 17: Type 2 Diabetes Mellitus in Childhood and Adolescence **147**
Ranjit Unnikrishnan, A Amutha, V Mohan

Chapter 18: Hypoglycemia **154**
Khalid Hussain
- *Importance of Diagnosis 154*
- *History 154*
- *Examination 155*
- *Symptoms of Hypoglycemia 155*
- *Investigations 156*
- *Differential Diagnosis of Hypoglycemia 157*
- *Treatment 157*

SECTION 7: ADRENAL DISORDERS

Chapter 19: Approach to Adrenal Insufficiency **163**
Palany Raghupathy
- *Clinical Manifestation of Hormonal Deficiency 163*
- *Classification 163*

- *Evaluation 164*
- *Investigations 165*
- *Treatment 165*

Chapter 20: Congenital Adrenal Hyperplasia **170**
Aparna Limaye
- *Approach to a Child with Congenital Adrenal Hyperplasia 170*
- *Approach to Clinical Evaluation 172*

SECTION 8: DISORDERS OF SEX DEVELOPMENT

Chapter 21: Disorders of Sex Development **179**
Garry L Warne
- *Case Walk: An Infant with Ambiguous Genitalia 180*

SECTION 9: SODIUM AND WATER BALANCE

Chapter 22: Disorders of Water Balance **191**
Anna Simon
- *Disorders of Increased Water Excretion: Diabetes Insipidus 191*
- *Disorders of Positive Water Balance: Syndrome of Inappropriate Antidiuretic Hormone Secretion 195*

Chapter 23: Disorders of Sodium Balance **198**
Sarah Mathai
- *Hypernatremia 198*
- *Hyponatremia 201*

SECTION 10: AIDS AND TOOLS

Chapter 24: Aids and Tools **209**
Nalini S Shah, Sudha Rao
- *Physiological Factors Affecting Hormonal Measurements 209*
- *Sample Collection and Handling of Some Hormones for Laboratory Assessment: General Guidelines 209*

Index *219*

CHAPTER

3 Growth Hormone Deficiency

Shaila Bhattacharya

CASE

An 8-year-old Shruti came for consultation in view of short stature. Her parents had noticed that she is short as compared to her peers since first standard and is not growing. She is an apparently healthy child with normal birth and developmental history. She is a playful active child and is good in studies. Her height is 105 cm (<< 5th centile) and weight is 20 kg (25–50th centile). The mid parental height (MPH) is 155 cm (25–50th centile). Her upper segment:lower segment (US:LS) ratio is 1:1. She has frontal bossing, mid-facial hypoplasia, large prominent eyes, small hands and feet. Her routine biochemistry [complete blood count (CBC), liver function test (LFT), renal function test (RFT), calcium profile, electrolytes, bicarbonate levels] were normal. Her BA is 5 years. Both insulin-like growth factor (IGF-1) and IGF binding protein (IGFBP-3) are low for her age. After confirming normal thyroid function tests (TFTs) and basal cortisol, she is subjected to growth hormone (GH) stimulation tests (clonidine and insulin induced hypoglycemia). The peak GH is 0.6 ng/mL and 0.5 ng/mL on the two tests respectively. Other anterior pituitary functions are normal. Her magnetic resonance imaging (MRI) of the pituitary hypothalamic region with contrast showed a hypoplastic anterior pituitary. Thus a diagnosis of idiopathic isolated growth hormone deficiency (GHD) was arrived in this patient.

GROWTH HORMONE PHYSIOLOGY

Pituitary growth hormone secretion is stimulated by growth hormone-releasing hormone (GHRH) from the hypothalamus. When growth hormone is secreted into the systemic circulation, IGF-1 is released, either systemically or at the site of growing bone. Growth hormone binds to a specific growth hormone-binding protein (GHBP). This GHBP is actually the extracellular portion of the growth hormone receptor. IGF-1 binds to one of several IGFBPs and circulates mainly (> 99%) in the bound state. IGFBP-3 accounts for most of the IGF-I binding and this binding protein directly depends on growth hormone.

JAYPEE BROTHERS

Magnitude of the Problem

The incidence of GHD is believed to be around 1 in 4,000 to 1 in 10,000. If around 100 children are evaluated for short stature only, 5–10 of them will have GHD.

Final height data in patients with untreated GH deficiency is around-4.7 standard deviation score (SDS). Besides short stature, GHD children have other morbidities, hence timely diagnosis and treatment is important.

Etiology

Approximately 25% of the children diagnosed with GHD have an underlying "organic" cause such as trauma, irradiation, tumors, etc. The remainder is labeled as idiopathic. Growth hormone deficiency can be isolated [isolated growth hormone deficiency (IGHD)] or associated with other hormone deficiencies CPHD (Box 1.3.1).

Box 1.3.1: Causes of growth hormone deficiency

Congenital
Genetic:
IGHD: GH1, GHRHR
CPHD: HESX1, SOX3, LHX3, LHX4, PROP1, POU1F1 (PIT1)
Associated with structural defects of the brain:
- Agenesis of the corpus callosum
- Septo-optic dysplasia
- Holoprosencephaly
- Encephalocele
- Hydrocephalus

Associated with midline facial defects:
- Cleft lip/palate
- Single central incisor
- Idiopathic

Acquired
Trauma: Perinatal/postnatal
Infection: Meningitis/rncephalitis
CNS tumors:
- Craniopharyngioma
- Pituitary germinoma
- Histiocytosis
- Following cranial irradiation
- Following chemotherapy
- Pituitary infarction

Transient:
Psychosocial deprivation
Peripubertal
Hypothyroidism

Keywords: CPHD, combined pituitary hormone deficiency; GH, growth hormone; GHRHR, growth-hormone-releasing hormone receptor; IGHD, isolated growth hormone deficiency

JAYPEE BROTHERS

EVALUATION

History

- Age: Growth hormone deficiency can present at any age. Prenatal growth in GHD is near normal although severe GHD can have decreased birth length
- Sex: Male and female: 3:1
- Height: Obtains all the previous records of height and plot them on the growth chart. The mid-parental height should also be marked. If the growth rate is normal (about 5 cm/year from age 4 years to puberty), the child's short stature most likely is caused by a normal variant, such as FSS or constitutional delay in growth and maturation. If the growth rate is slow, a pathological cause for short stature is more likely
- A child who has been growing along the 75th centile but moves across to the 25th centile warrants investigation even though his/her height may still be within normal range
- Systemic disorders: Before evaluation of GH axis it is necessary to rule out chronic medical illness that can give rise to short stature. Malnutrition is a common cause of short stature worldwide. Other causes are chronic anemia, congenital heart disease, chronic renal failure (CRF), chronic infections and inflammation, bronchial asthma, renal tubular acidosis (RTA) and chronic liver disease
- Those with intracranial space occupying lesions can have headache, vision defects or other features of raised intracranial tension. It is imperative to enquire regarding cranial irradiation, trauma, chemotherapy or neurosurgery. Temperature disturbances, polyuria, polydipsia, polyphagia and somnolence are suggestive of hypothalamic involvement
- Birth history: CPHD can present with neonatal hypoglycemia or prolonged neonatal jaundice. Breech delivery is common in CPHD. GHD with gonadotropin deficiency can lead to micropenis, cryptorchidism and hypoplasia of the scrotum
- Family history: Growth hormone deficiency can be familial in 10–20% of the cases. It is important to ask whether there is history of delay in growth and maturation in the parents to distinguish GHD from CDGP.

Examination

- Height and weight: During first 2–3 years of life, length should be measured with an infantometer. After 2–3 years of age, height should be measured on a wall-mounted, well-calibrated ruler with an attached horizontal measuring bar fixed at 90°, e.g. a stadiometer. The child should stand erect, with the back of the head, back, buttocks area, heels touching the vertical bar of the stadiometer and the horizontal measuring bar is lowered to the child's head to obtain the measurement
- In addition to height, weight measurement will provide clues toward the etiology of short stature. Normal or elevated weight SDS, points toward

JAYPEE BROTHERS

endocrine disorders like Cushing's syndrome or pseudohypoparathyroidism while low weight SDS points toward systemic illnesses. Weight:height ratios tend to be increased, and fat distribution is often "infantile" or "doll-like" in pattern. Central adiposity is relatively less marked in Indian children (Figs 1.3.1A and B).

- Proportions: The US:LS ratio in normal baby at birth is approximately 1.7:1 and decreases to 1:1 at age 10 years, a ratio that lasts throughout adulthood. Skeletal proportions tend to be relatively normal in GHD, but correlate better with BA than with chronologic age
- Other phenotypic features: Delayed dentition may be observed in GHD, but in the absence of midline craniofacial abnormalities, it is otherwise normal and not of much significance. Other skeletal appearances include hypoplasia of facial bones, hypoplastic nasal bridge, frontal bossing and delayed closure of sutures. Head circumference is usually at the lower limits of normal, indicating normal brain growth. The voice is infantile because of hypoplasia of the larynx. Hair growth is sparse and thin, especially during early life; nail growth is also slow (Figs 1.3.1A and B).
- Pubertal status: The stage of puberty is assessed by the Tanner's method of sexual maturity rating. Orchidometer is used for accurate measurement of testicular volume. Puberty is usually delayed even in isolated growth hormone deficiency (Fig. 1.3.2).

Investigations

Baseline Screening Investigations

Following tests should be done to rule out any underlying systemic illness (Table 1.3.1).

- Bone age = CA > HA: Familial short stature, skeletal dysplasias and chromosomal anomalies.
- Bone age = HA < CA: CDGP, Malnutrition, GHD, Hypothyroidism, Chronic diseases, etc.

Table 1.3.1: Screening investigations of growth hormone deficiency

Cause of short stature	*Tests*
Malabsorption syndromes	CBC, albumin
Celiac disease	IgA, IgA tTG
Chronic infections/inflammatory conditions	ESR, tuberculin test, chest X-ray
Chronic renal disease	Serum creatinine
Distal RTA	Blood gas analysis
Chronic liver disease	Liver function tests
Hypothyroidism	T3, T4, TSH
Pseudohypoparathyroidism, Rickets	Serum calcium, PO4, PTH, radiology

Keywords: CBC, complete blood count; ESR, erythrocyte sedimentation rate; IgA tTG, IgA antibodies to tissue transglutaminase; PTH, parathyroid hormone; RTA, renal tubular acidosis.

JAYPEE BROTHERS

- Insulin like growth factor-1 and IGFBP-3: Low values of IGF-1 and IGFBP-3 suggest GHD. However, a low value alone is not diagnostic because IGFs are sensitive to other factors such as nutritional state and chronic systemic disease
- Growth hormone stimulation tests: Between normal pulses of GH secretion, serum GH levels are low (often < 0.1 ng/mL). Accordingly, measurement of random serum GH concentrations is virtually useless in diagnosing GHD. The diagnosis of GH deficiency classically rests on the demonstration of subnormal GH responses to two or more provocative pharmacologic tests of GH reserve (i.e. a GH peak less than 5 ng/mL, indicative of complete deficiency, and 5–10 ng/mL, indicative of partial deficiency). Provocative tests of GH reserve include arginine, l-dopa, clonidine, glucagon and insulin-induced hypoglycemia. Two pharmacologic tests are used traditionally because approximately 15–20% of apparently normal children have a poor response to a given single test of GH reserve. Appropriate priming with sex steroids prior to GH stimulation is required in peripubertal age
- Other pituitary axes: Thyroid function tests, cortisol estimation and gonadal axis evaluation may be required if clinically indicated. Child should be euthyroid before performing GH stimulation tests. In some of the patients, initially diagnosed as isolated GHD, other pituitary hormone deficiencies may evolve over a period of time. This requires careful monitoring on follow-up
- Magnetic resonance imaging: A cranial MRI scan with contrast of the hypothalamic-pituitary region should be carried out in any child diagnosed as having GHD. It will exclude any intracranial space occupying lesion and may show hypoplasia of the pituitary, ectopic posterior pituitary or stalk interruption in idiopathic GHD
- Karyotype: Girls with otherwise unexplained short stature should have a karyotype study to rule out Turner's syndrome even in the absence of other signs of Turner's syndrome.

Differential Diagnoses

Different clinical diagnoses are shown in Table 1.3.2.

Diagnostic Algorithm GHD/Growth Hormone Intensity (GHI)

Diagnostic algorithm GHD and GHI is given in Box 1.3.2.

Treatment

In children whose epiphyses are not yet fused, GH replacement usually causes significant increase in growth velocity (averaging 10–11 cm/year during first year of therapy). A single daily subcutaneous injection of recombinant growth hormone is given in the dose of 0.18–0.35 mg/kg of body weight per week. Response to growth hormone therapy is measured (every 3–6 months) by sequential height determinations and by occasional BA determinations.

JAYPEE BROTHERS

Table 1.3.2: Different clinical diagnoses

Cause of short stature	*Clinical pointers*
Systemic disorders (malnutrition, CRF, chronic liver disease, chronic infections, congenital heart disease, etc.)	Anemia, edema, underweight, lymphadenopathy, hepatospleenomegaly
Constitutional delay in growth and puberty	Similar family history, delayed growth spurt
Hypothyroidism	Weight gain, bradycardia, dry skin, goiter
Pseudohypoparathyroidism	Obese, short fourth metacarpals
Rickets	Wrist widening, double malleoli, rosary, frontal bossing, knee deformity
Skeletal dysplasia	Short trunk or short limbs, low nasal bridge, incomplete ossification of spine
Cushing's syndrome	Round facies, facial plethora, virilization
Turner, Noonan syndromes	Delayed puberty, shield-shaped chest, cubitus valgus, short webbed neck, lymphedema hands and feet
Silver-Russell syndrome	Triangular facies, clinodactyly,
Prader-Willi syndrome	Obese, hypotonia, feeding difficulties
Psycho social short stature	Signs of neglect or abuse

Box 1.3.2: Diagnostic algorithm GHD and GHI

Step 1: Defining the risk of IGF deficiency syndrome

Auxologic abnormalities
- Severe short stature (height SDS < – 3 SD)
- Severe growth deceleration (height velocity SDS < –2 SD over 12 months)
- Height < –2 and height velocity < –1.0 SD over 12 months
- Risk factors
- History of a brain tumor, cranial irradiation, or other documented organic or congenital hypothalamic-pituitary abnormality

Step 2: Screening for IGF deficiency and other diseases

Bone age, free T4, and TSH, karyotype (in females), screening tests and IGF-I, and IGFBP-3 level

Step 3: Testing GH secretion

Perform two of the following GH stimulation tests (if appropriate, sex steroid priming)
- Clonidine
- Arginine
- Insulin
- Glucagon
- L-Dopa (L-3,4-dihydroxyphenylalanine)
- Propranolol

If all GH levels are below 10 ng/mL, go to step 4

Step 4: Evaluating the pituitary

- Perform MRI with contrast, with particular emphasis on hypothalamic-pituitary anatomy

Step 5: Treating for growth promotion

- Initiate GH treatment at appropriate dose levels
- Regularly evaluate growth parameters, IGF-I and IGFBP-3, as well as compliance and safety

JAYPEE BROTHERS

KEY MESSAGES

- Growth hormone deficiency is one of the rare causes of short stature
- Rule out systemic illnesses
- Try to gather all the previous growth records
- Growth hormone stimulation tests to be done in correct manner with priming if required.

SUGGESTED READING

1. GH Research Society: Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. J Clin Endocrinol Metab. 2000;85(11):3990–3.
2. Ron G Rosenfield, Pinchas Cohen. Disorders of growth hormone/insulin like growth factor secretion and action. Pediatric Endocrinology, Sperling, 3rd edition. Philadelphia; Saunders Elsevier. 2008.

JAYPEE BROTHERS



Figs 1.3.1A and B: Growth hormone deficiency. (A) 9-year-old male presented with short stature, cherubic infantile facies, preserved truncal fat and small genitals; (B) Typical facies with bossing of skull, shallow orbit, depressed nasal bridge



Figs 1.3.2: GHD with short stature, micropenis, preserved truncal pad of fat, infantile facies

JAYPEE BROTHERS

IAP Specialty Series On

PEDIATRIC ENDOCRINOLOGY

This book *IAP Specialty Series on Pediatric Endocrinology* helps provide a clinical approach to common pediatric endocrine disorders. The various sections addressed by experts in the field cover common Pediatric Endocrine problems seen in a general pediatric clinical practice. Each topic is elucidated with case scenarios and provides an algorithm to its clinical approach and management. This book is designed so as to be used as a clinician's handbook rather than a reference textbook.

Conceptualized by
IAP National Publication House, Gwalior
iap.publication@gmail.com

Available at all medical book stores
or buy directly from Jaypee Brothers through online shopping
at www.jaypeebrothers.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
www.jaypeebrothers.com

Shelving
Recommendation
PEDIATRICS

ISBN 978-93-5090-365-0