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Atlas of Growth and Endocrine Disorders in Children



Prisca Colaco

JAYPEE

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CHAPTER 4

Growth Hormone Deficiency

The estimated frequency of growth hormone deficiency (GHD) is 1 in 3,500–10,000. Untreated final height is 134–146 cm in males, and 128–134 cm in females.

- GHD may be:
  - Isolated growth hormone deficiency (IGHD)—70–80% or
  - Combined with other pituitary hormone deficiencies (CPHD)—deficiency of two or more pituitary hormones
- About 3 to 30% of cases (in different studies) of GHD are familial (Fig. 4.1).

ETIOLOGY OF GROWTH HORMONE DEFICIENCY

- Idiopathic
- Congenital:
  - Anatomic—midline defects
  - Genetic
    - Isolated growth hormone deficiency:
      - Autosomal recessive: IGHD 1A and1B, bioinactive GH, growth-hormone-releasing hormone receptor (GHRHR) defects
      - Autosomal dominant: IGHD II
      - X-linked: IGHD III
    - Combined with other pituitary hormone deficiency (Table 4.1):
      - Autosomal recessive: LHX3, PROP1
      - Autosomal dominant: LHX4
      - AR/AD: HESX1, POU1F1 (PIT1)
      - X-linked recessive: SOX3.
- Acquired:
  - Tumors of the hypothalamus or pituitary
  - Trauma
  - Irradiation
  - Infiltration
  - Infection.

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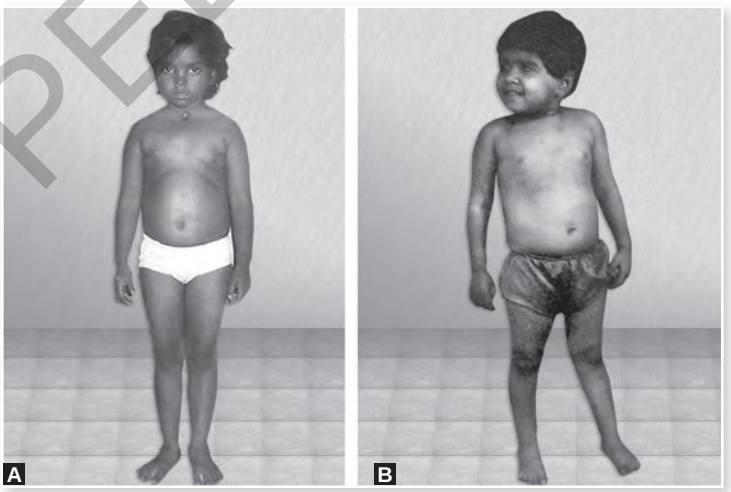
TABLE 4.1: Combined pituitary hormone deficiencies

LHX3	Deficiencies of GH, TSH, LH, FSH, PRL, rigid neck, small/N/enlarged anterior pituitary
LHX4	Deficiencies of GH, TSH and ACTH, small anterior pituitary cerebellar and skull defects
HESX1	Panhypopituitarism, optic nerve hypoplasia, agenesis of the corpus callosum, ectopic posterior pituitary
PROP1	Panypopituitarusm except ACTH deficiency, small/normal/or enlarged anterior pituitary
POU1F1 (PIT1)	Deficiencies of GH, TSH, PRL, small or normal anterior pituitary
SOX3	Hypopituitarism, mental retardation, learning difficulties, small anterior pituitary, ectopic posterior pituitary



Figs 4.1A to C: Familial growth hormone deficiency: (A) Siblings with CPHD-GH and Thyrotropin deficiency. Girl 12-year prepubertal; 15-year boy: G3 P3; (B) Father and daughter with GH deficiency and normal mother; (C) Aunt and nephew with CPHD (the boy's parents were normal)

Acquired Growth Hormone Deficiency (Figs 4.2 and 4.3)



Figs 4.2A and B: (A) A 9-year old girl with GHD postcranial irradiation; (B) A 6-year-old with GHD following TB meningitis

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Growth Hormone Insensitivity (Fig. 4.3)

- Group of diseases characterized by marked short stature with normal or elevated GH concentrations, which fail to respond to exogenous GH administration
- Clinically indistinguishable from GHD cases
- Autosomal recessive disorders associated with defects in the GHR gene (Laron syndrome) or post-GHR defects: IGF-1 deficiency and IGF-1 resistance, primary ALS deficiency or signal transducer and activator of transcription 5B (STAT5b) deficiency
- IGF-1 and GH binding protein (GHBP) levels depend on the mutations:
  - IGF-1 low in all except IGF-1 resistance (high)
  - GHBP: normal in all except in mutations in the extracellular domain of GHR (low)
- Except for IGF-1 resistance, respond well to treatment with recombinant human IGF-1.



Fig. 4.3: Siblings, 11 years and 4 years of age, with GH insensitivity

CLINICAL EVALUATION

Clinical features of GHD depend on whether GHD is:

- Congenital or acquired
- IGHD or CPHD
- On the severity of deficiency.

History

- Onset of growth retardation—depends on the etiology
- Birth weight and length—usually normal. May be small in some congenital forms with complete absence of GH–GH gene del
- Perinatal factors (often associated with CPHD)—breech delivery, prematurity, gestational bleeding, fetal distress, birth asphyxia

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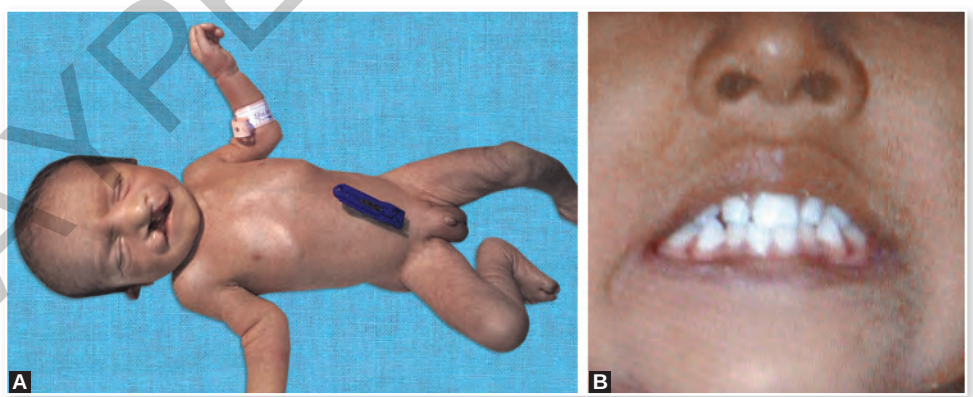
- Neonatal manifestations:
  - Hypoglycemic manifestations
  - Prolonged neonatal jaundice
  - Micropenis
- Family history—Consanguinity, other affected family member
- History of cranial irradiation, intracranial infections, trauma, symptoms of raised ICT.

Clinical Features (Fig. 4.4)

- Short stature—usually severe <-3SD by the time of presentation. Shorter than 2SDs below midparental percentile. Body proportions normal
- Growth velocity is <25 centile and usually <4 cm/year
- Chubby appearance—truncal obesity, increased skinfolds, decreased lean body mass
- Doll-like facies—head appears round with frontal prominence; midfacial hypoplasia—small nose, eyes appear large
- In boys the genitalia may appear small
- Small hands and feet
- High pitched voice
- Midline defects—cleft lip/palate, single central incisor may be associated (Figs 4.5A and B)
- Delayed dentition
- Delayed or absent puberty
- Signs of other pituitary hormone deficiencies including diabetes insipidus
- Neurologic abnormalities, nystagmus, visual impairment, squints, optic nerve hypoplasia in septo-optic dysplasia.



Fig. 4.4: 5-year-old boy with the classic phenotype of GHD



Figs 4.5A and B: Clinical clues to the diagnosis of hypopituitarism: (A) Cleft palate and micropenis in a newborn; (B) Single central incisor

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INVESTIGATIONS

Bone age estimation: Bone age delayed >2SD for age. May be more affected in CPHD than IGHD

Prior to evaluation of the GH-IGF-I axis other causes of short stature should be ruled out.

s. IGF1, insulin-like growth factor-binding protein 3 (IGFBP3): <-2SD for age, sex and pubertal stage.

Random growth hormone levels are not useful in the diagnosis of GH deficiency as GH secretion is pulsatile.

GH stimulation tests (Table 4.1): In a child with clinical criteria for GHD, a peak GH concentration below 10 ng/mL (20 mU/L) on two standard provocative tests, has traditionally been used to support the diagnosis. These include arginine, clonidine, glucagon, insulin, and l-dopa. For organic GHD only one provocative test may suffice.

Patients should be adequately replaced with other deficient pituitary hormones before testing for GH secretion. All stimulation tests are performed after an overnight fast and involve measuring serum growth hormone levels.

Table 4.1: Growth hormone provocation tests

Stimulus	*Dosage*	*Samples (minutes)*
Insulin IV*	0.05–0.1 unit/kg	0, 15, 30, 60, 90, 120
Clonidine PO	0.1–0.15 mg/m^2 (max 0.25 mg)	0, 30, 60, 90
Levodopa PO	<15 kg: 125 mg 15–30 kg: 250 mg >35 kg: 500 mg	0, 60, 90
Arginine infusion	0.5 g/kg (up to 20 g)	0, 15, 30, 45, 60
Glucagon IM	0.03 mg/kg (up to 1 mg)	0, 30, 60, 90, 120, 150, 180

*Blood glucose should fall at least 50%. Risk of hypoglycemia.

Sex steroid priming: 10 µg ethinyl estradiol PO daily × 3 days or 100 mg testosterone IM 3 days before the test in children >8 years who are prepubertal or in early puberty.

Testing in the neonate: Random GH levels in newborns range from 5–40 ng/mL. Random GH >10 ng/mL indicates adequate GH secretion. If random levels are low stimulation tests with GHRH or glucagon may be done, but their interpretation in newborns is unresolved. Stimulated levels should be >25 ng/mL in newborns. GH should always be measured in the presence of neonatal hypoglycemia in the absence of a metabolic disorder. GH<20 ng/mL at time of hypoglycemia suggests insufficiency. An IGFBP-3 measurement is the best test for suspected GHD in a neonate. IGF-1 is of no value.

IGF-I/IGFBP-3 generation test is required for the diagnosis of GH insensitivity.

Tests for other pituitary hormone deficiencies: LH, FSH, TSH (low FT4; low TSH), ACTH (Low 8 am cortisol without a rise in ACTH; Poor response to CRH/ ITT) PRL, ADH.

MRI (Figs 4.6 and 4.7): Height/volume of the pituitary gland; anatomy of the stalk and position of posterior pituitary; empty sella; size of optic nerve and optic chiasm; developmental anomalies; acquired lesions—intracranial tumors, e.g. craniopharyngioma, germinoma.

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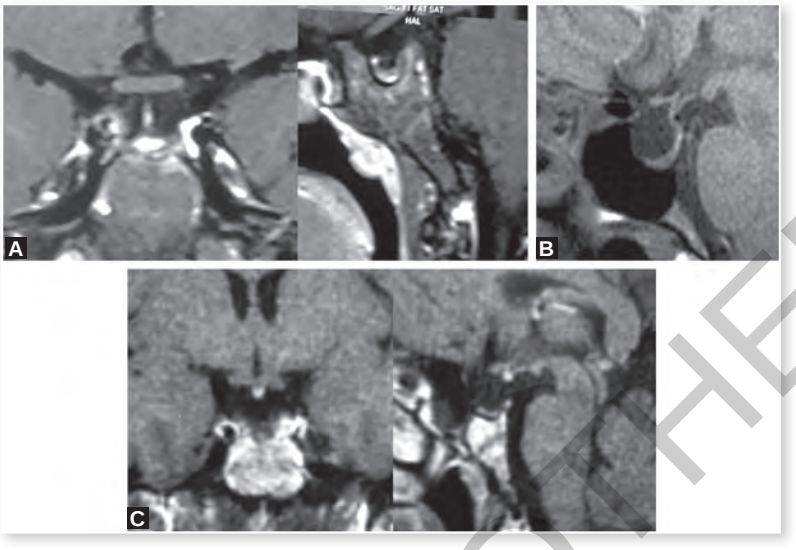
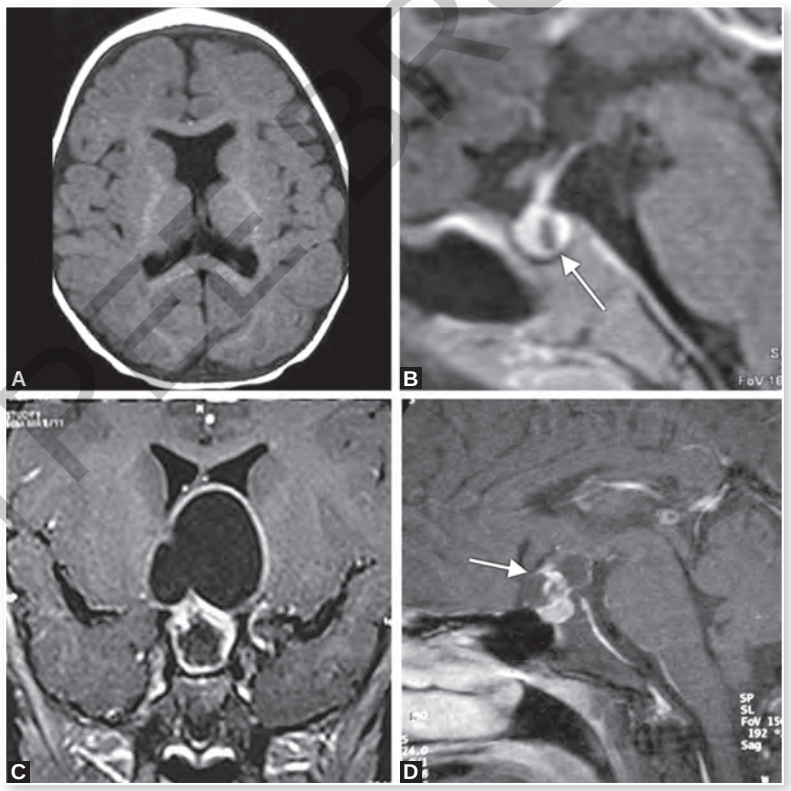


Figs 4.6A to C: MRIs in idiopathic GHD: (A) Small pituitary gland 2.5 mm height. Posterior pituitary and stalk normal; (B) Empty sella; (C) Ectopic posterior pituitary



Figs 4.7A to D: MRI in organic causes of GHD: (A) Septo-optic dysplasia; (B) Rathke's cleft cyst; (C) Craniopharyngioma; (D) Pituitary tumor (prolactinoma) (*Courtesy*: Dr Sudha Rao)

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TREATMENT

Indications for GH Therapy

The child has signs or symptoms of growth hormone deficiency such as growth velocity <2 SD below mean for age or height <2.25 SD below mean for age and

1. A subnormal response (<10 μg/mL) to any two standard growth hormone stimulation tests.
   OR
2. Neonates with hypoglycemia and clinical and hormone evidence of hypopituitarism (growth hormone level <10 μg/mL).
   OR
3. Documented presence of at least two other pituitary hormone deficiencies, in addition to IGF-1 measurement below age-appropriate level.
   OR
4. Children who have had cranial irradiation and have documented evidence of IGF-1 measurement below age-appropriate level with normal thyroid function tests results.

Goal of Treatment

To achieve normal height during childhood and to attain normal adult height.

Dose

Growth hormone should be administered in the evening daily as a subcutaneous injection in the dose of 25–50 μg/kg/day. The dose has to be individualized depending on the growth response.

In children with CPHD, cortisol should be initiated before thyroxine and GH.

Response to Therapy

Maximal response is seen in the first year of treatment with growth velocities generally 200% of the pre-treatment velocity, and then gradually waning over the subsequent years to average 150% of the baseline. Height improvements of 1 SD are typically achieved in children with GHD after two years of treatment, and between 2 and 2.5 SD after five or seven years.

As height with GH therapy should be maximized before the onset of puberty, modifying puberty by the use of GnRH analogues and aromatase inhibitors has been advocated by several investigators.

IGF1 levels must be monitored and maintained within the normal range.

Treatment is continued until final height is attained or epiphyseal closure has been recorded. Adult GH replacement should be started after retesting the individual and continued throughout adulthood though at significantly lower "adult" doses, for its metabolic effects and to achieve normal peak bone mass.

Side Effects of Growth hormone Therapy

- Pseudotumor cerebri
- Arthralgia

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- Edema
- Insulin resistance-generally transient and reversible
- Hypothyroidism
- Adrenal insufficiency
- Transient gynecomastia
- Scoliosis is more common in Turner syndrome and PWS
- Pancreatitis-in patients with Turner syndrome, and associated risk factor
- Sleep apnea/sleep disturbance—in patients with Prader-Willi syndrome
- No association has been found between rhGH and leukemia, increased recurrence risk of CNS tumors in children without predisposing conditions, or slipped capital femoral epiphysis (SCFE).

rhIGF1 Treatment

This treatment has been approved by the FDA for children with:

1. Severe primary IGF1 deficiency
2. GH gene deletions who have developed neutralizing antibodies to GH.

SUGGESTED READING

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Atlas of Growth and Endocrine Disorders in Children

Salient Features

- Early diagnosis and proper management of pediatric endocrine disorders is essential, as these conditions have far reaching consequences not only during childhood, but also impact eventual adjustment to adulthood
- This book has been written for the practising pediatrician and provides a simple clinical approach to the diagnosis and management of all the commonly encountered pediatric endocrine disorders, including disorders of calcium and glucose homeostasis
- Written in an easy-to-read format, it is heavily illustrated with clinical photographs and charts to enable easy diagnosis and appropriate management.



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