Diagnosis of growth hormone deficiency (GHD) in pediatric patients

Growth hormone (GH)

Peptide hormone that stimulates growth, cell reproduction and cell regeneration and has metabolic effects

Secreted into circulation by somatotrophs (cells of the anterior pituitary; Figures 1 and 2) in a pulsatile manner, regulated by both hypothalamic and peripheral factors.This is GH as an endocrine hormone

Endocrine GH targets the liver, bones, adipocytes and muscles and activates molecular signaling pathways in these tissues (Figure 2)

Also secreted in an autocrine/paracrine manner and acts in multiple tissues

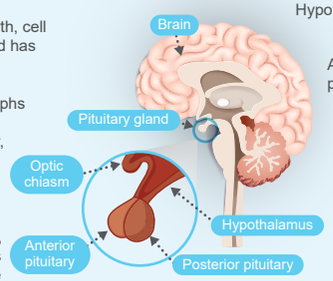


Figure 1. Anatomy of the pituitary

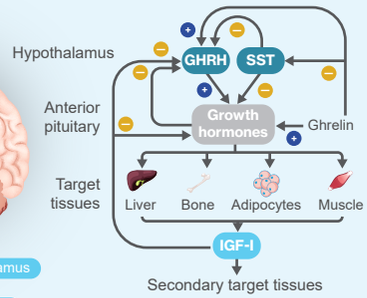


Figure 2. Signaling pathways of the hypothalamic-pituitary axis. GHRH, growth-hormone-releasing hormone; IGF-I, insulin-like growth factor I; SST, somatostatin

Growth hormone deficiency (GHD)

A rare cause of growth failure; can be congenital or acquired

1:3500 children have GHD[1]

2 : 1 male to female ratio of pediatric patients in GH registries or referred to endocrine clinics (despite an equal prevalence of severe short stature in males and females)[2]

~85% of patients receiving GH treatment are white (exceeding expected frequencies based on US census and growth rates)[3]

Early diagnosis of GHD and earlier initiation of GH treatment increases adult height outcomes

5 cm/year – the average growth rate of children during mid-childhood[4]

<4 cm/year – the definition of growth failure in children during mid-childhood[4]

Diagnosing GHD

The following criteria, indications and assessments can help with the diagnosis of GHD, but each has its limitations:

Anthropometric criteria

Height more than 2 standard deviations (SD) below the mean for age and gender in the local population

Height more than 2 SD below mid-parental height

Abnormally slow growth velocity

Downwardly crossing major height centiles on the growth chart

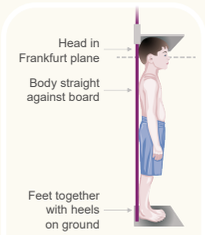


Figure 3. Correct measuring technique

Limitations

Only 30% of pediatric height measurements are accurate (within 0.5 cm of the actual height)[4]

Observational study of 55 US primary care practices: average measurement inaccuracy was ±1.3 cm, which can result in improper or missed diagnosis of growth problems, such as GHD[4]

Patient history and physical examination

Patient history:

Mid-parental height (note: this is a range)

Delayed puberty

Neonatal period – presence of hypoglycemia, jaundice and/or microphallus

Central nervous system and mid-line defects

Cranial insult

Physical examination:

Increased body fat

Eyes: nystagmus and funduscopic examination

Teeth: central maxillary incisor

Mid-face hypoplasia

Tanner staging of puberty

Limitations

Failure to attain mid-parental height does not always indicate GHD

Some children have constitutional delay of growth regardless of GHD

Combination of constitutional delay superimposed on familial short stature can appear more worrisome than it is

IGF-I and IGF-binding protein 3 (IGFBP-3) blood tests

Circulating concentrations of IGF-I and IGFBP-3 reflect spontaneous GH secretion[7]

Unlike GH, IGF-I and IGFBP-3 levels do not change with time of day

Limitation

IGF-I and IGFBP-3 levels are affected by nutritional status, GH action, age, puberty, renal and hepatic function, and diabetes status

Bone age radiographs

Can be used to predict adult height

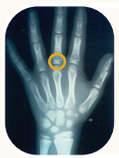


Figure 4. Bone age is determined by assessing the maturation of the epiphyses (such as the one highlighted by the yellow circle)

Limitation

Poor agreement across different methods of predicting adult height[6]

Pituitary magnetic resonance imaging

Can detect the presence of structural aberrations and screen for tumors

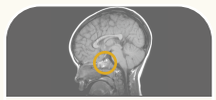


Figure 5. Magnetic resonance image showing the position and normal appearance of the pituitary

Limitation

Cannot distinguish abnormalities at the cellular or molecular level

Provocative GH testing

GH secretory response is assessed using reagents that stimulate GH secretion (secretagogues)[8]

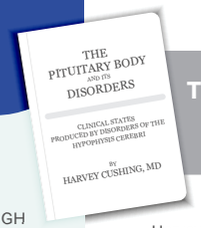
Two independent tests should be conducted to overcome the high false-failure rate

Commonly used secretagogues include insulin, arginine, clonidine, L-DOPA and glucagon

Limitation

Provocative GH tests are non-physiologic, lack precision, have inter-assay variability, and are invasive and expensive

The history of GHD and its treatment[5]



- **1912** – Harvey Cushing associated pituitary abnormalities with short (and tall) stature and hypothesized that the pituitary secreted a 'hormone of growth'
- **1921** – Role of the pituitary in growth first proven by the injection of extracts from anterior lobes of bovine pituitary glands into rats
- **1943, 1944** – Purification and isolation of bovine GH
- **1958** – First patient with GHD treated with human GH
- **1962** – Amino acid sequence of GH elucidated
- **1971** – Primary structure of GH determined
- **1985** – Recombinant human GH first produced (somatrem, metGH)
- **1986** – Recombinant human GH produced (somatropin, rhGH)

PES guidelines on the diagnosis and treatment of GHD[9]

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Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency

Adda Grimberg, Sara A. DiVall, Constantin Polychronakos, David B. Allen, Laurie E. Cohen, Jose Bernardo Quintos, Wilma C. Rossi, Chris Feudtner, Mohammad Hassan Murad on behalf of the Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society

"Strongly recommend against the reliance on GH provocative test results as the sole diagnostic criterion of GHD"

"Suggest sex steroid priming prior to provocative GH testing in prepubertal boys older than 11 and in prepubertal girls older than 10 years with adult height prognosis within –2 SD of the reference population mean in order to prevent unnecessary GH treatment of children with constitutional delay of growth and puberty"

Unmet needs with current diagnostic techniques

- IGF-I and IGFBP-3 assays should be standardized and harmonized. Use of somatropin standard IRP IS 98/574, 22k rhGH isoform is recommended to harmonize GH assays
- Lack of standardized provocative GH test protocols and diagnostic thresholds
- Need for new secretagogues that result in consistent secretion of GH
- Genomics, proteomics, metabolomics and new imaging techniques may support the diagnosis of GHD in the future

PES Pediatric Endocrine Society

References

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GHD knowledge center