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

**Growth hormone deficiency (GHD)**

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

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

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

Unmet needs with current diagnostic techniques

IGF-I and IGF-Binding protein 3 (IGFBP-3) assays should be standardized and harmonized. Use of somatomedin standard IRP 98/574, 22k IGF-I isoform is recommended to harmonize GH assays

Lack of standardized provocative GH test protocols and diagnostic thresholds

Need for new secretagogues or secretagogues that result in consistent secretion of GH

Geranios, proteomics, metabolomics and new imaging techniques may improve the diagnosis of GHD in the future

**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
- Downward crossing major height centiles on the growth chart

**Patient history and physical examination**

- **Patient history:**
  - Mid-parental height (note: this is a range)
  - Delayed puberty
  - Neonatal period: absence of symptoms of hypothyroidism, jaundice and/or microcephaly
  - Central nervous system and mid-line defects
  - Cranial insult

- **Physical examination:**
  - Increased body fat
  - Eyes: nystagmus and funduscopic examination
  - Teeth: central and 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 GH
- 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
- Unlike GH, IGF-I and IGFBP-3 levels do not change with time of day

**Provocative GH testing**

- GH secretory response is assessed using reagents that stimulate GH secretion (secretagogues)
- Two independent tests should be conducted to overcome the high false-failure rate
- Commonly used secretagogues include insulin, arginine, clonidine, L-Dopa and glucagon

**Pituitary magnetic resonance imaging**

- Can detect the presence of structural abnormalities and screen for tumors
- Magnetic resonance image showing the position and normal appearance of the pituitary

**Limitations**

- Cannot distinguish abnormalities at the cellular or molecular level

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**Prognostic and treatment of GHD**

Purification and isolation of bovine GH

First patient with GHD treated with human GH

Amino acid sequence of GH elucidated

Recombinant human GH first produced (somatrem, metGH)

Recombinant human GH produced (somatropin, rGH)

Primary structure of GH determined

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

References

8. Ranke M. Diagnosis of growth hormone deficiency and growth hormone elevation tests. In: Diagnosis of Endocrine Failure