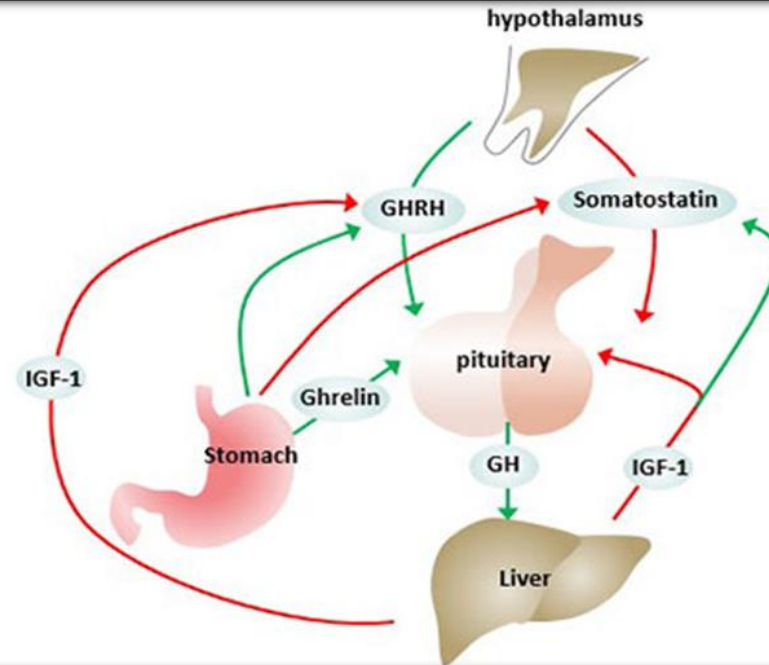# Diagnosis of GH deficiency

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# Objectives

- Introduction of short stature.
- Indications of GHD investigations?
- GH testing:
  - Physiological.
  - Pharmacological.
- Newer strategies for assessment of GH status (using GHRH).
- Sex – steroid priming for GH provocative tests.
- The IGF/ IGFBP system in childhood.
- International Criteria for the diagnosis of GHD.

# GH Gene

- The human genome contains five GH-related genes:
  - human growth hormone (hGH).
  - human chorionic growth prolactin-A.
  - human chorionic growth prolactin-B.
  - human chorionic growth prolactin-like.
  - human auxin variant.
- They have the same transcriptional direction but are separated by a 6-13 kb long gene interval.
- The five genes have about 90- 99% sequence homology, and each gene contains 5 exons and 4 introns.
- The five genes are grouped together to form a gene cluster, which is located on the long arm q22-24 of chromosome 17.

# Physiological secretion of GH

- GH is secreted in a pulsating manner, and its secretion has fluctuation, with the largest change range at night and the most vigorous secretion at puberty, and then gradually decreases with the increase of age.

- The secretion of growth hormone in pituitary gland is controlled by two hypothalamic peptides: GH releasing hormone (GHRH) and somatotropin release inhibiting factor (SRIF).

- GHRH is the main regulatory factor of GH, which promotes the transcription and release of GH gene.

- Somatostatin inhibits the secretion of growth hormone by inhibiting the growth nutrition response of growth hormone to GHRH.

- The third factor is Ghrelin, which stimulates growth hormone secretion, although its role in physiological regulation of growth hormone secretion is controversial.

# Growth Hormone Functions

- Human growth hormone has a wide range of physiological functions.

- HGH mainly affects the growth, metabolism and differentiation of cells by affecting the growth axis of GH-IGF1, promotes protein synthesis.

- Increase Muscle Strength.

- The release of growth hormones is crucial to regulating bone growth, especially during puberty.

- Increased height in childhood is one of the most important roles of growth hormone.

- GH activates the MAPK/ERK pathway by binding to receptors on target cells and stimulates the division and proliferation of chondrocytes.

- Human growth hormone speeds bone regeneration, making it a key part of bone healing.

- HGH can promote the breakdown of fat in animals.

- Impaired secretion of human growth hormone will result in loss of lipolytic function.

- Insulin resistance and visceral/abdominal obesity are common in adults with hormonal growth defects.

- Human growth hormone can play a therapeutic role in helping obese people lose weight.

# Growth Hormone Functions

- Studies have shown that growth hormone deficiency can alter lipoprotein metabolism and increase the risk of cardiovascular disease.
- Growth hormone plays a vital role in mental and emotional health and maintaining high energy levels.
- Adults with growth hormone deficiency are more likely to suffer from depression.
- Studies have shown that growth hormone therapy in adults with growth hormone deficiency can improve their cognitive function and mood.
- Growth hormone can regulate immune function, increase thymocyte activity, affect B cell development and function, and enhance NK killing activity.
- Growth hormone is involved in the development, differentiation and functional integration of brain neurons.
- Numerous studies have shown that growth hormone can stimulate the regeneration of neurons, astrocytes, endothelial cells and oligodendrocytes, as well as the formation of myelin sheath and dendritic diversity.

# Indications of GH stimulation test

- Standing height > 2 SD below the mean for chronological age, sex & ethnic background.

- Growth velocity < 5 cm / year.

- Children with decelerating growth even they are still on normal percentiles.

- Children with delayed BA.

- Children who have hypothalamic-pituitary dysfunction (e.g., microphallus, septo-optic dysplasia, intracranial tumor, history of cranial irradiation).

- Children who have deficits in other hypothalamic- pituitary hormones (congenital or acquired).

# GH testing

- Physiological
- Pharmacological

# Growth Hormone physiological secretion

- GH is a single chain polypeptide of 191 amino acid residues with two disulphide bridges.
- Secreted by the anterior pituitary gland under the control of GHRH, somatostatin & Ghrelin.
- GH is secreted in approximately 8 peaks /day with low basal levels in between these pulses.
- Nearly 50 % of the daily GH secretion occurs during the early hours of the night following the onset of deep sleep.
- Various pharmacological & physiological factors are potent stimulators of GH secretion:
  - Exercise, stress, high protein meal & prolonged fasting.

# The IGF system in childhood

- The IGFs are related GH-dependent peptide factors believed to mediate many of the anabolic and mitogenic actions of GH.

- The serum level of the major GH-dependent peptide IGF-1 is stable during the day, due mainly to the complexing of IGF peptides with a family of IGF-binding proteins (IGFBPs).

- The potential for assessing GH status with a single estimation of the circulating IGF-1 level proved attractive and gave rise to the hope that eventually dynamic GH provocation tests may become unnecessary.

- Children & adolescents with variety of illnesses & metabolic disorders have altered circulating IGF-1 & IGFBP levels.

- Exogenous obesity, anorexia nervosa, celiac disease, leukemia, other types of cancer & GH deficiency, this axis can be altered.

- Some reported cases of children with non- detectable levels of circulating IGF-1 that yet normal height and growth velocity, or with non-detectable levels of GH yet normal growth & IGF-1 levels, raises many questions marks.

- Additional problems remain, including lack of specificity.

- The IGF-1 level is influenced markedly by age & pubertal development.

- Use of age & puberty-corrected IGF-I values improves the diagnostic use of IGF-1.

- Low concentrations of IGF-I occur in normal children < 5 years of age.

- To have better use of IGF-1 in the screening test, should be done along with IGFBP3.

# IGFBPs

- Of the six known IGFBPs, IGFBP-3 is normally the major serum carrier of IGF peptides.

- IGFBP-3 circulates as part of a ternary complex consisting of IGFBP-3, IGF peptide & acid-labile subunit.

- Both acid-labile subunit & IGFBP-3 are GH dependent.

- Age dependency of IGFBP-3 is less striking than for IGF-1.

- Similarly, the influence of nutritional status on IGFBP-3 levels is less than for IGF-1 level.

- Low IGF-1 & IGFBP-3 concentrations are reliable guides to the diagnosis of severe GHD, providing the investigator the alternative possibilities of malnutrition, hypothyroidism, liver disease & GH insensitivity.

# GH secretion physiological assessment

- GH secretion assessment by physiological circumstances e.g., exercise test, 24-h GH profiling & urinary GH estimation in the diagnosis of GHD.

- The exercise test is safe, simple to perform as an outpatient procedure and inexpensive.

- Unfortunately, an absent GH response to exercise may occur in up to 1/3 of normal prepubertal children (i.e., 33% false positive).

  - The exercise test, however, is no longer used in clinical practice.

# Pharmacological GH testing

# GH provocation testing

- There is considerable variability in the different types of assay used to measure GH, so each laboratory needs to set its own threshold for defining GHD.

- This adds to the difficulty & variability in the diagnosis of GHD worldwide.

- Generally, a peak GH response of < 20 mU/L or < 10ng/ml is considered evidence of GHD.

- There are also, false positive & negative results with any of these tests so that "normal" children with normal growth patterns can fail to have good GH response on single agent of pharmacological testing

- The first established pharmacological stimulus introduced for assessment of GH status was insulin tolerance test (ITT).

- Advantages of this test include:
  - ACTH-adrenal axis can be assessed at the same time.
  - Considered to be a powerful stimulus to GH release.
  - Induces moderate hypoglycemia, which is sufficient to elicit maximal GH responses.

- The main disadvantages include:
  - Lack of normative data in children, a characteristic it shares with many other pharmacological tests.
  - Unpleasant nature of the test, which in inexperienced hands is frankly dangerous.

- Other pharmacological stimuli were introduced afterward including:
  - L-dopa , Arginine , glucagon , propranolol, Clonidine , GHRH & Pyridostigmine.
- A variety of combinations of these tests has been used.
- In some centers, two provocative stimuli are administered sequentially or in combination.
- Combination approach may be time-saving & more economical.
- No evidence to suggest, the results are more meaningful if the tests were performed in combination rather than individually.

# Assessment of GH status (using GHRH)

- The effects of the commonly used provocative tests of GH release, such as arginine, clonidine & ITT, are mediated through activation of α- receptors in the hypothalamus.

- The availability of GHRH provides strong means of assessing the secretory capacity of the pituitary somatotroph directly.

- The use of GHRH in combination with substances that act via inhibition of endogenous somatostatin, such as pyridostigmine (cholinesterase inhibitor) & arginine, has been explored to provoke a much greater GH response than other agents used in GH combined stimulation tests.

# International Criteria of GHD

- Standing height >2 SD below the mean for chronological age, sex & ethnicity.

- GV ≤ 4 cm/year (prepubertal).

- BA ≥ 2 years behind CA.

- Low IGF-1 & BP3.

- Subnormal GH secretion in response to at least two provocative stimuli when sampled over several hours.

- Increased IGF1 levels after few days of GH treatment.

- Increased growth velocity after few months of GH treatment.

Thanks