Effects of hypersecretion of GH

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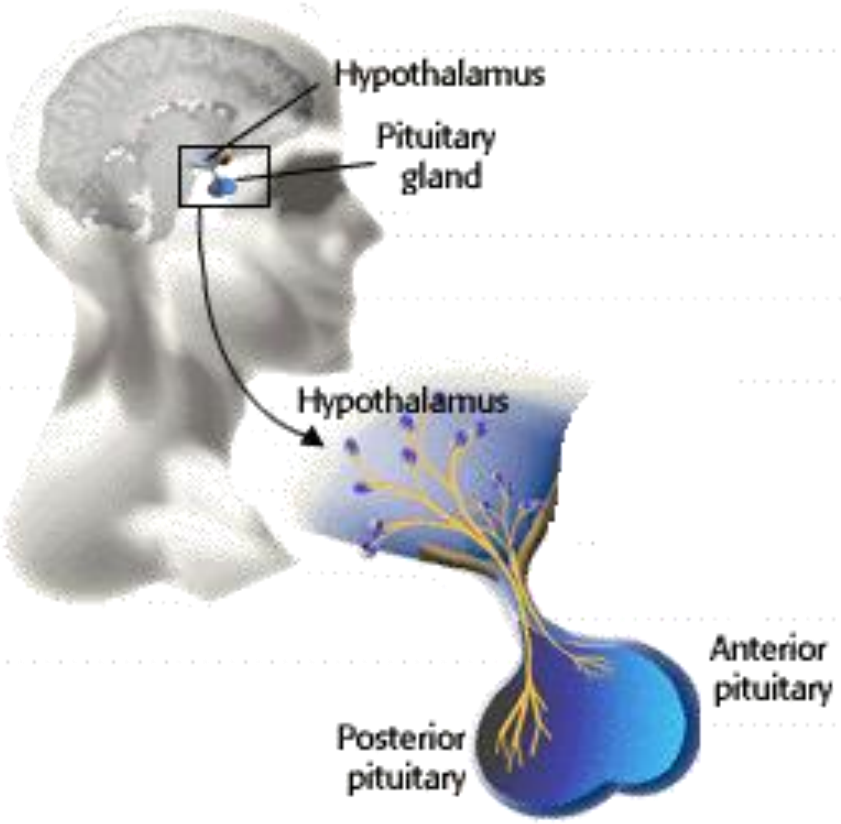
Introduction

- The human adult pituitary weighs approximately 0.5g, not larger than size of a pea, exerts a pivotal role in hormonal regulation of various bodily processes
- The pituitary gland is responsible for the production of 8 hormones
- It is largely regulated by the hypothalamus
- The anterior pituitary accounts for about 75% of its weight

- The pituitary composed of 2 lobes:
  - anterior lobe “ adenohypophysis”
  - posterior lobe “neurohypophysis”



What is Growth Hormone? (Somatotropin)

- GH is a protein hormone of 190 amino -acids that is synthesized & secreted by the acidophil cells of the anterior pituitary gland
- It is a major participant in control of several complex physiologic processes, including growth & metabolism
- The major role of growth hormone in stimulating body growth is to stimulate the liver and other tissues to secrete IGF-I
- IGF-I stimulates proliferation of chondrocytes (cartilage cells), resulting in bone growth

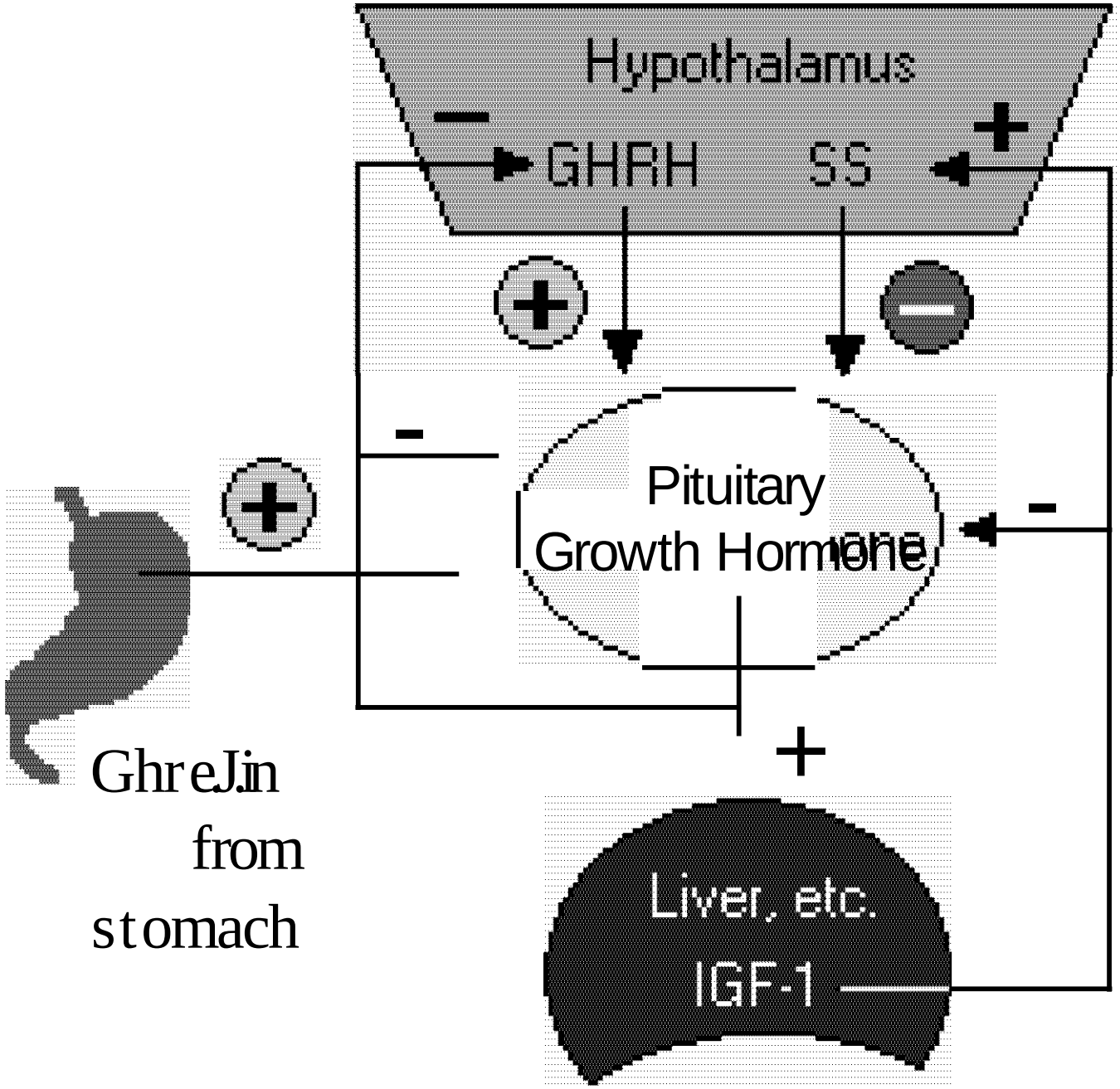
- IGF-I also appears to be the key player in muscle growth, stimulates both the differentiation &proliferation of myoblasts
- It also stimulates amino acid uptake and protein synthesis in muscle and other tissues
- Growth hormone has important effects on protein, lipid &carbohydrate metabolism
- Production of growth hormone is modulated by many factors, including stress, exercise, nutrition& deep sleep

Control of Growth Hormone Secretion

It is primary under control of (2) hypothalamic hormones & one hormone from the stomach

1. **Growth hormone-releasing hormone** (GHRH) is a hypothalamic peptide that stimulates both the synthesis & secretion of growth hormone
2. **Somatostatin hormone inhibits growth hormone release**
3. **Ghrelin**

peptide hormone secreted from the stomach which binds to receptors on somatotroph & potently stimulates secretion of growth hormone

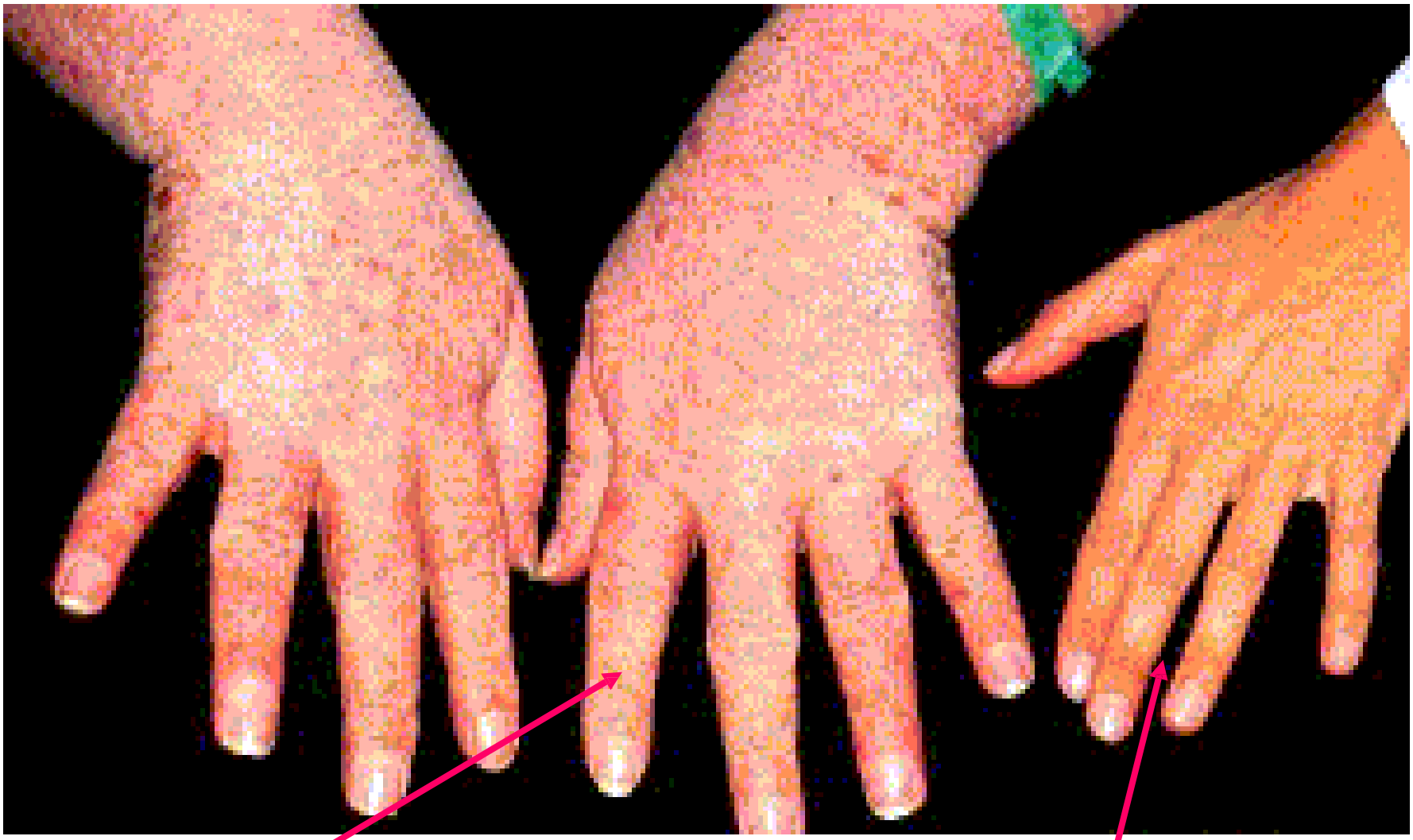

Hypothalamus
GHRH
SS
Pituitary
Growth Hormone
Ghrelin
from
stomach
Liver, etc.
IGF-1

Effects of GH hypersecretion Gigantism or Acromegaly

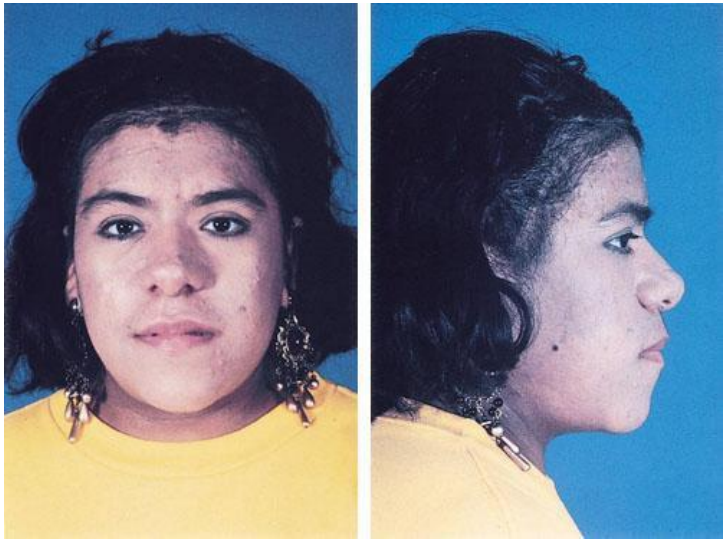
- Acromegaly / Gigantism is a very rare disease (annual incidence: 3/1.000.000)
- Gigantism results from increased GH secretion during childhood
- Acromegaly results from overproduction of GH after puberty in adults
- At puberty, the epiphyseal plates of the long bones close, so they become unresponsive to GH stimulation, However, this is not the case of the hands, feet, skull and lower jaw
- they continue to grow, resulting in the distinctive physical appearance of an acromegaly patients

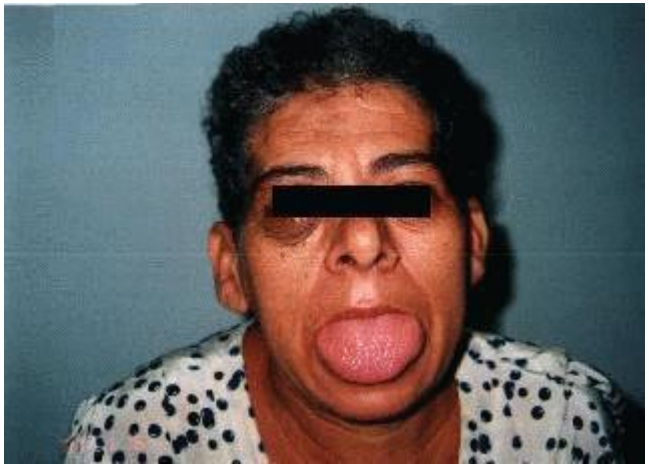
Clinical features

- Excessive growth makes the child extremely large for his or her age
- Delayed puberty
- Double vision or difficulty with side (peripheral) vision
- Frontal bossing & prominent jaw
- Headache
- Increased sweating
- Irregular periods (menstruation)
- Large hands & feet with thick fingers and toes
- Release of breast milk (galactorhea)
- Weakness


Acromegaly Hands
Normal Hand

- Facial changes
  - Coarsening of features
  - Prognathism
  - Diastema)widely spaced teeth(
- Acral enlargement
  - Increased ring &shoe sizes
  - Hands become enlarged, moist &soft
  - Tufting of distal phalanges
- Skin changes
  - Generalized thickening
  - Increased sweating &oiliness –an important sign of activity of the disease
  - Hypertrichosis, Acanthosis nigricans & acne



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- Respiratory Disease
  - Upper Airway Obstruction (Caused by Soft Tissue Overgrowth)
  - Sleep Apnea
- Malignancy
  - Colon, Esophagus, Stomach, Polyps
  - Melanoma
  - Lymphoma
- Endocrinopathy (due either to GH excess or to mechanical effects of the adenoma)
  - Hyperprolactinemia
  - Diabetes Mellitus / Carbohydrate intolerance
  - Hypogonadism
  - Hypothyroidism
  - Hypoadrenalism
  - Decreased libido or impotence

- Visceromegaly
- Neuropathies & Arthropathy
  - Carpal Tunnel Syndrome
  - Peripheral neuropathy & paresthesia
  - Spinal Cord or nerve root compression from bony overgrowth

- Local Effects of Pituitary (mass effect)
  - Headache; visual impairment, hypopituitarism, rhinorrhea
- Cardiovascular disease
  - Cardiomyopathy left ventricular diastolic function decreased; Left ventricular hypertrophy; arrhythmia & Hypertension

One of the most famous giants was a man named Robert Wadlow
Robert reached an adult weight of 490 pounds and 8 feet 11 inches in height, He died at age 22

Causes

- The most common cause is GH secreting Pituitary adenomas which are often over 1cm in diameter when the diagnosis is established
- Rarely is due to a microadenoma
- About 15% of GH secreting tumors also hypersecrete Prolactin, explaining the clinical manifestation of hyperprolactinemia also seen in these patients

Other causes include:

- McCune-Albright syndrome (MAS)
- Multiple endocrine neoplasia type 1 (MEN-1)
- Neurofibromatosis

Investigations

- CT or MRI scan of the head showing pituitary tumor
- Failure to suppress serum growth hormone (GH) levels after an oral glucose challenge (maximum 75g)
- High prolactin levels
- Increased insulin growth factor-I (IGF-I) levels
- Damage to the pituitary may lead to low levels of other hormones, including:
  - Cortisol
  - Estradiol (girls)
  - Testosterone (boys)
  - Thyroid hormone

- Diagnosis can be made from the characteristic clinical findings
- CT, MRI, or skull x-rays disclose:
  - cortical thickening, enlargement of the frontal sinuses, enlargement & erosion of the sella turcica
- X-rays of the hands show tufting of the terminal phalanges and soft-tissue thickening
- Generally, glucose tolerance is abnormal

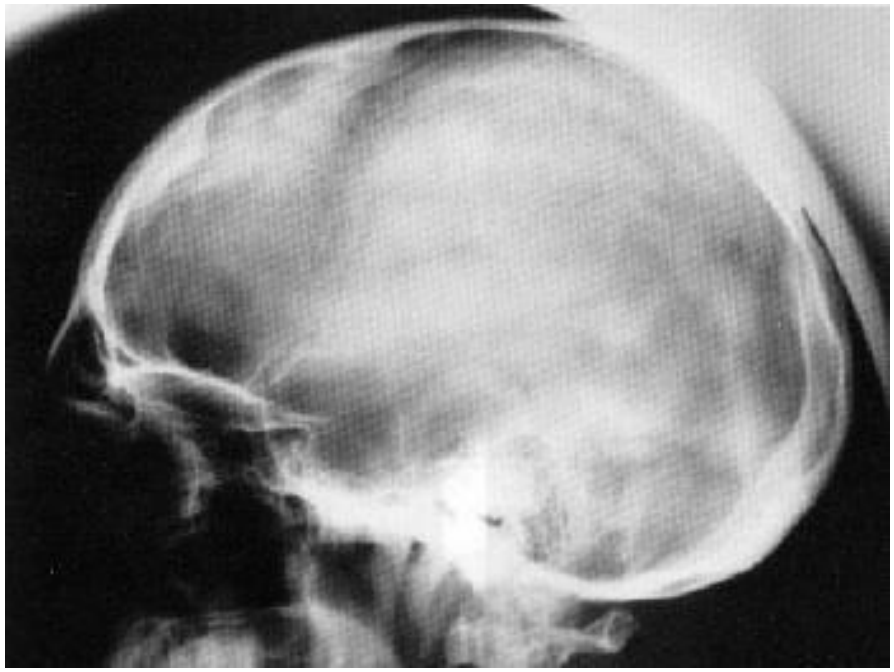
- CT or MRI of the head should be performed to look for a tumor
- If a tumor is not visible, excessive secretion of pituitary GH may be due to a non-CNS tumor producing excessive amounts of ectopic GHRH
- Demonstration of elevated levels of plasma GHRH can confirm the diagnosis
- Lungs & pancreas may be first evaluated in searching for the sites of ectopic production

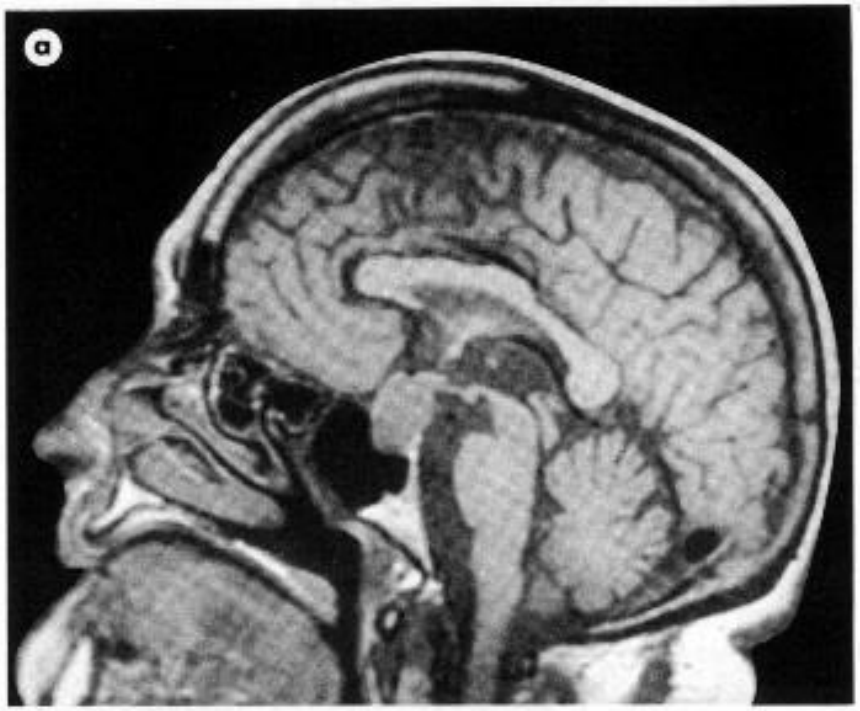
Tumor Localization

- In all patients, MRI (90% have more than 1cm in diameter) can show tumor localization and size
- The finding of a normal MRI is very rare
  - In this case, the next procedure is considering an extra-pituitary ectopic source of GHRH or GH
- If the scans suggest diffuse pituitary enlargement or hyperplasia, ectopic GRH should be suspect

Heel Pad Measurement

- Usually more than 22mm & must be measured with lateral X - Ray

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Treatment

1. Surgical therapy

- This is the gold standard of GH-secreting tumors because of its aggressive behavior
- Should be done as the primary choice in all patients who are otherwise acceptable surgical risks
- The surgical modality can be trans-sphenoidal (the better) or craniotomy (in case of extrasellar enlargement of the adenoma)

2. Radiation therapy

- The main disadvantage of this therapy is the long-term duration to reach the „goals of therapy
- About 5 years are required for reduction of GH levels to normal in 50% of the patients
- Side effects of this therapy are the development of pan-hypopituitarism in 15-15% of the patients with a lag time from less than 1 - 10 years

Medical Therapy

- Two medications are currently used: (Medical therapy is sometimes used to shrink large tumors before surgery)
  - Dopaminergic Analogues
- Bromocriptine
  - In at least 50% of acromegalic, dopamine action is presumably through a dopamine D2 receptor mediated mechanism, thus suppressing GH secretion
  - Side effects include GH upset, nausea, vomiting, light headedness when standing and nasal congestion
- Somatostatin analogues (Octreotide)
  - As explained below with the use of dopaminergic analogues, the use of octreotide also depends on the presence of somatostatine receptors in the adenoma
  - 10-30% of acromegalic has low density of these receptors.
  - This drug must be injected under the skin every 8 hours

Other conditions of overgrowth or excessive tallness in childhood

1) Children who are excessively tall are often referred to as Giantigionists
2) Early onset of obesity results in above-average growth in mid-childhood, such that over half of overweight children have heights in the 70 - 99 percentile range at around 10 years of age
3) Precocious puberty and a variety of conditions associated with excessive amounts of testosterone or estrogen in childhood will result in tallness by mid-childhood
4) Chromosomal / Karyotype disorders
   - The most common of these karyotypes are 47,XXY (Klinefelter syndrome), 47,XYY, and 47,XXX

5) Marfan syndrome is an uncommon genetic disease due to an inherited defect of connective tissue

- In addition to moderate tallness, persons with this condition usually have a slender body build with unusually long fingers (arachnodactyly)
- Many can also develop a dislocaton of the lens of the eye or, more seriously, a progressive deterioration of the walls of the aorta which can result in sudden death in adulthood
- It is usually inherited as an autosomal dominant trait

6) Sotos syndrome resembles acromegaly in its mild distortion of facial growth

- In addition to tallness, the chief characteristics are
  - large head size, slow development, and autosomal-dominant inheritance

7) Hypogonadism is the condition of deficiency of sex hormones due to reduced function of the testes or ovaries at adolescence




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