Hypothalamus & pituitary

The hypothalamus and pituitary gland are key regulators of the hormone system.
Sensory and endocrine information is processed and integrated in the brain.

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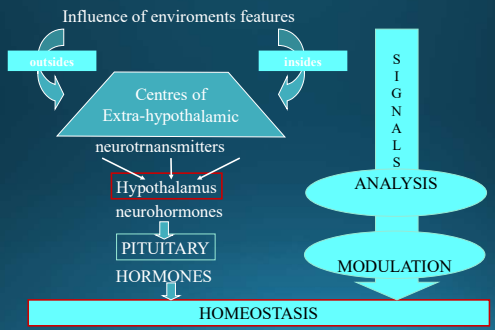
The role of hypothalamo-pituitary system



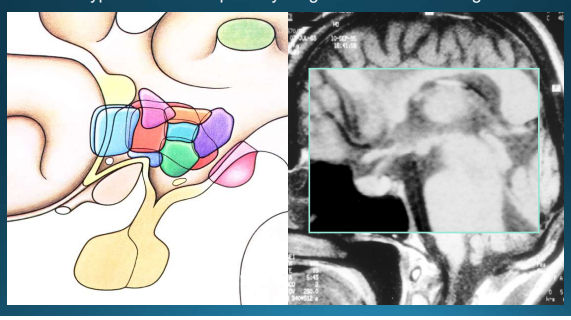
Endocrine disorders

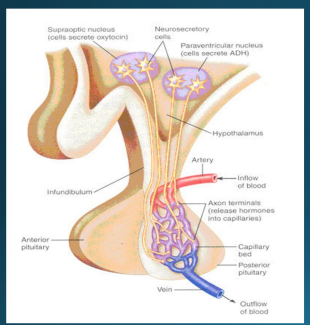
Manifest in one of ways:

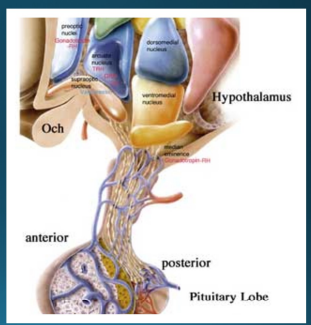
- by excess hormone
- by deficient hormone
- by abnormal response of end organ to hormone

Diagram of human hypothalamus

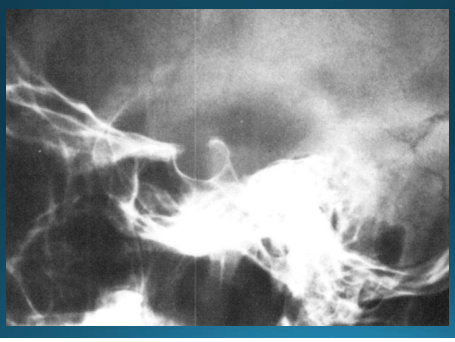
The hypothalamic and pituitary magnetic resonance images







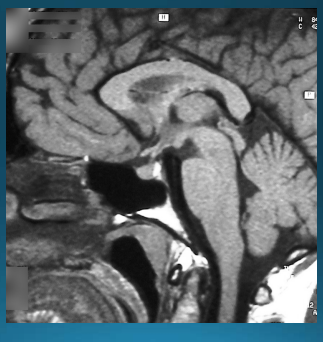
RTG sella turcia(„Turkish saddle")

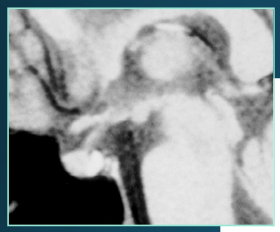


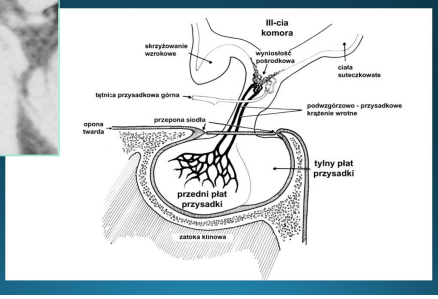
MR

The composition of H atoms
= „MAP"

water fat







The role of hypothalamus

The centres
Regulates the sympathetic actions
Body temperature, food intake, circadian rythm, thirsty

Neurohormones

+	-
TRH	SRIH
GnRH	DA
CRH	
GHRH	
VIP	

Hormones
Vasopressin (ADH)
oxytocin

Hypothalamic hormones

Posterior pituitary hormones
(synthetized in large cell bodies supraopic nuclei and lateral and superior paraventricular nuclei)

- **Vasopressin (ADH)**- regulator of water balance
- **Oxytocin**- regulator of milk ejection from mammary gland

Hypothalamic hormones (Hypophyseotropic hormones 1)

Hypophyseotropic hormones
regulate the secretion of anterior pituitary hormones

- GHRH- Growth Hormone Releasing Hormone (GHRH)
  (secreting cells are located in the arcuate nuclei): stimulates growth hormone (GH) secretions by somatotrophs
- Somatostatin (SRIH)
  (secreting cells are located in the periventricular region above the optic chiasm)
  inhibits the secretion of GH and TSH

Hypothalamic hormones (Hypophyseotropic hormones 2)

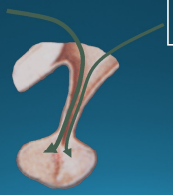
- Dopamine
  (dopaminergic system are located in the arcuate nuclei)
  inhibits prolactin (PRL)
  Prolactin releasing factors- is: TRH
- Thyreotropin Releasing Hormone (TRH) *(secreting cells are located in medial portions of the paraventricular nuclei)*
  stimulates TSH thyreotropin hormone secretion
- Corticotropin-Releasing Hormone (CRH)
  (secreting cells are located in anterior portions of the paraventricular nuclei)
  stimulates ACTH – adrenotropic hormone secretion

Hypothalamic hormones (Hypophyseotropic hormones 3)

- Gonadotropin-Releasing Hormone (GnRH)
  (secreting cells are located in preopic area of the anterior hypothalamus)
  stimulates **LH (luteinizing hormone)** and
  FSH (follicule-stimulating hormone) hormone secretion

Hypothalamic dysfunctions

pituitary insufficiency
- in adults hypogonadism,
- in children- short stature
- hypothyroidism
- adrenal insufficiency



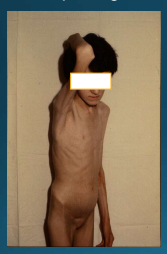
DIABETES INSIPIDUS

Hypothalamic dysfunction- clinical features

- Disorders of consciousnes
- Disorders of behavior
- Disorders of thirst
- Disorders of appetite
- Disorders of temerature regulations
- Disorder in circadian rythm (somnolence)
- Diabetes insipidus
- Pituitary insuffiency-(decreased levels of pituitary hormones)
- Visual field defects

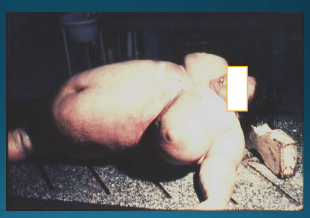
Hypothalamic dysfunction

Craniopharingioma



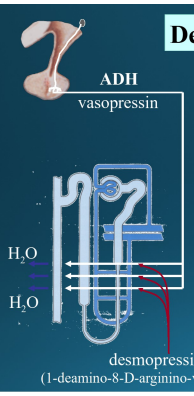
24 kg

Sarcoidosis



240 kg

Definition



Diabetes insipidus

Deficient of ADH
Characterized by the passage of copious amounts of very dilute urine (urine weight <1,005g/ml) leads to loss of large volumes of dilute urine (>8-10 l/24hours.) retiremented after desmopressin acetate requirement

Diabetes insipidus (neurogenic, central or cranial DI)

- Prevalence 1:25,000
- Most often in patients udergoing pituitary surgery or in other forms of neurosurgical intervention (18-30% of cases in the first 2 days; in next 2-5 days)

Hypothalamic DI

Congenital: hereditary (X-linked or AD)

DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy)

Pituitary surgery

Tumors (craniopharyngioma, germinoma, pinealoma, metastases)

Traumatic brain injury

Granuloma

Infection

Vascular disorder

Hypophysitis

Idiopatic

Pregnancy

Diabetes insipidus (DI) in children

DI is due either to

- deficient secretion of ADH by the pituitary **gland (central or neurogenic DI)**
- renal tubular unresponsiveness to vasopressin **(nephrogenic DI).**

Causes of DI

Nongenetic causes

- Nongenetic causes of DI include injuries. Typical injuries include head trauma, tumor, and neurosurgical procedures. At all ages, destructive lesions of the pituitary, the hypothalamus, or both are the most common cause of DI.

Genetic causes

- **Central DI** with an autosomal dominant pattern inheritance is due to a mutation in the prepro-arginine vasopressin (*prepro-AVP2*) gene, mapped to locus 20p13. Central DI with diabetes mellitus, optic atrophy, and mental retardation (Wolfram syndrome) may be inherited in an autosomal recessive pattern (locus 4p16) or may be due to mitochondrial deletions.
- **X-linked nephrogenic DI** occurs from mutations in the antidiuretic arginine vasopressin V2 receptor (*AVPR2*) gene, mapped to Xq28. Nephrogenic DI with an autosomal dominant or recessive pattern is due to mutations in the gene designated *AQP2*; this gene directs water channel formation in the distal membrane and has not yet been mapped.

Paediatric DI

Central DI:
Congenital – Less common
VP-ANP Gene defect (Chr 20p13)
Familial Autosomal Dominant DI (more common)
Familial Autosomal Recessive DI
WFS1 gene defect (Chr4p16) – DIDMOAD syndrome
Congenital Anatomic defect
Septo-optic-dysplasia
Holoprosencephaly
Agenesis of corpus callosum
Kabuki Syndrome
Familial pituitary hypoplasia
Infundibulum defect
Others
Vasopressinase excess
Syndrome of defective Osmoregulation
Acquired – More common
Primary tumors or metastasis
Germinoma, Pinealoma, Craniopharyngioma, Glioma
Pituitary stalk thickening
Infections / Infiltrative lesions
Meningitis / Encephalitis
Granulomatosis, Tuberculosis, sarcoidosis
Histiocytosis, Hemochromatosis, Amyloidosis
Drugs Phenytoin, Carbamazepine, Valproic acid, adrenergic drugs
Trauma / Surgery
Autoimmune disorders (rare)
Hypoxic encephalopathy
Idiopathic – 10-25% of cases
Nephrogenic DI – More common in children
Congenital
X linked NDI –Xq28 encoding AVPR2
Autosomal Recessive NDI –Ch 12q13 encoding AQP2
Autosomal Dominant NDI
Acquired – More common
Drugs
Lithium, demeclocycline, amphotericinB, rifampin, methicillin
Hypercalcemia / Hypokalemia
Primary renal diseases
Polycystic kidney disease, ureteral obstruction, uremia etc.
Primary Polydypsia
Psychogenic
Dipsogenic
DI: Diabetes insipidus

	Central DI	Nephrogenic DI
Age at presentation	Infancy/between 5-6 yrs/rarely adulthood	Antenatal hydramnios/ neonatal age/early infancy
Incidence	Rare	Common
Etiology	Often acquired cause	Mostly acquired cause
Mode of inheritance	AD/AR	X-linked/AD/AR
Gene	AVP NPII; WFS-1	AVPR2, AQP2
Clinical presentation	Marked thirst Growth failure	Severe thirst Failure to thrive Growth failure Mental retardation
Mental retardation	Rare	++
Basal urine osmolality	Low	Low
Basal plasma osmolality Osm	Normal/Low	Low
Post WDT urine osmolality	Low	Low
Post WDT plasma osmolality	High	High
Post WDT SAVP levels	Low or inappropriately normal	High
Response to dDAVP	Very good	Poor
MRI Posterior pituitary bright signal	Absent	May be present
Long term Prognosis	Congenital: Good Acquired: depends on etiology	Short stature, mental retardation commonly seen.

DI: Diabetes insipidus, AD: Autosomal dominant, AR: Autosomal recessive, WDT: Water deprivation test, SAVP: Serum arginine vasopressin, dDAVP: 1-deamino-8D-arginine vasopressin; MRI: Margentic resonance imaging

DI in children

- Diabetes Insipidus (DI) is a heterogeneous clinical syndrome of disturbance in water balance, characterized **by polyuria (urine output > 4 ml/kg/hr), polydypsia (water intake > 2 L/m²/d) and failure to thrive.**
- Polyuria, defined as quantified urine output of more than **4 ml/kg/hr in children (more than 6 ml/kg/hr in neonates) and polydypsia, defined as water intake of more than 2 L/m²/d (or more than 5 L/d)** and failure to thrive or growth retardation are essential features of DI

DI in children

- The initial step in the diagnosis of DI is to ascertain the presence of polyuria (24 hours urine output measurement either by direct collection or indirectly by weighing the diaper in smaller children and infants).
- Urine output more than **4 ml/kg/hr in infants and children and more than 6 ml/kg/hr in newborn is suggestive of polyuria.**
- Once polyuria is established, it is necessary to rule out **solute diuresis i.e glucosuria, hypercalciuria or uremia by urine analysis and biochemistry.** Measurement of serum potassium and calcium concentrations is also important to exclude the possibility of polyuria secondary to hypokalemia or hypercalcemia.

DI in children

- **Presence of polyuria in the absence of solute diuresis should raise the suspicion of DI**.

CDI and NDI could manifest as partial or complete forms.

- The first morning urine specific gravity is a useful screening test and urinary specific gravity of more than 1.010 makes the diagnosis of DI less likely. In young infants, finding a distinction between normal and pathological inability to concentrate urine may be difficult because infants generally exhibit a constitutional hyposthenuria.
- Early morning measurement of simultaneous serum osmolality, urine osmolality and serum electrolyte is essential in pediatric age group while assessing a case of suspected DI. Urine osmolality of more than 800 mOsm /kg with a serum osmolality of less than 270 mOsm/kg rules out the diagnosis of DI, **whereas dilute urine with an osmolality of less than 300 mOsm/kg, and a serum osmolality of more than 300 mOsm/kg effectively establishes the diagnosis.**

DI in children

- If the initial serum osmolality **is less than 300 mOsm/kg,** a water deprivation test is done to confirm the diagnosis and 1-deamino-8D-arginine vasopressin (dDAVP) test is done to distinguish between CDI and NDI. Measure of post water deprivation osmolality is an "indirect test" of vasopressin sufficiency, whereas measurement of vasopressin (AVP) levels post water deprivation is a "direct test" of vasopressin action. Water Deprivation Test (WDT) is a potentially life threatening test and should be performed only in the centers with expertise

Various studies suggest that the combination of the water deprivation test and direct AVP determination would allow the diagnosis of more than 95% of all cases of DI correctly

Wadia Protocol

Preparation

- Stop all fluid intake at midnight (or later in infants or in patients who are polyuric or borderline hyperosmolar). Commence the restriction in the morning in children less than 2 years of age.
- Baseline weight to be recorded prior to the test and 5% of body weight is calculated.
- If suspected adrenal insufficiency give hydrocortisone 4 hours prior to test as cortisol is required for excretion for water.
- Thyroid and adrenal reserve must be normal or adequately replaced.

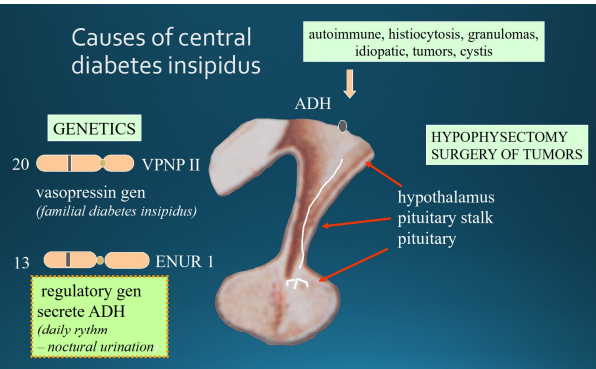
Protocol

- The night before the test, take blood for urea, electrolytes and serum and urine osmolality. If the serum osmolality is greater than 300 mOs/kg or serum sodium is more than 150 meq/l, the water deprivation test must not be undertaken.
- If the test is to proceed, weigh the patient undressed, record the weight and insert a reliable intravenous cannula.
- At 8 am, weigh the child again undressed and record the weight. Collect blood and urine for osmolality. Send specimens immediately to the laboratory.
- Continue to weigh the child hourly and check the vital parameters, for signs of dehydration/ hypovolemia and assess for hypoglycemia especially in infants.
- The test is continued until 7 hours of deprivation or either:-
  - The urine osmolality exceeds 750 mOsm/kg (or 500 mOsm/kg in infants);
  - 5% of initial weight is lost;
  - signs of hypovolemia are present;
  - plasma osmolality exceeds 300 mOsm/kg;
  - It may be necessary to prolong the test in compulsive water drinking, especially if the child has been drinking excessively immediately prior to the start of the test.
- When the test is terminated, take blood samples for urea, electrolytes, blood sugar, serum osmolality, urine osmolality and AVP levels.
- Allow the child to drink but not excessively. Fluid intake should be no more than twice the volume of urine passed during fluid restriction.
- Give aqueous vasopressin (pitressin) 5 U/m² subcutaneously, or dDAVP 10µg intranasally, or dDAVP 0.5 µg /m² sunbutaneously.
- Collect urine samples for osmolality hourly (if possible) for the next 4 hours.

Caveats

- Stopping test too soon based on body weight before either urine osmolality has plateaued above 600 mOsm/kg, or serum osmolality above 300 mOsm/kg, is a common error and should be avoided. Unless serum osmolality rises above threshold for vasopressin release, lack of vasopressin action as inferred by a non concentrating urine cannot be termed pathologic.

Causes of central diabetes insipidus

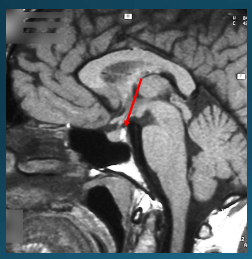


Treatment and conclusion

- Desmopressin is the drug of choice for CDI therapy, the oral formulation being more preferred.
- Treatment of NDI is essentially to treat the underlying cause, and drugs like thiazide, indomethacin help decrease water excretion.
- DI is not a very common pediatric endocrine disorder and NDI is more common than CDI.
- Water deprivation test is useful in establishing a diagnosis of DI and helps differentiating between NDI and CDI

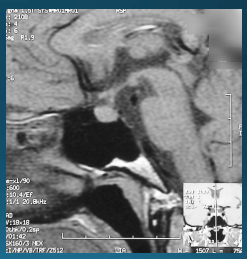
MR in diabetes insipidus

Normal posterior lobe „lights"



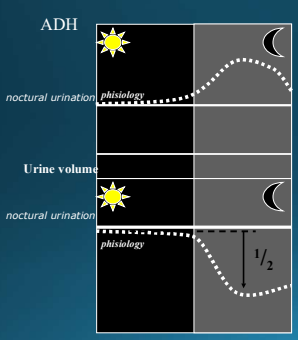
ADH secretion- normal

No signals from posterior lobe



Diabetes insipidus (autoimmune)

Vasopressin daily rythm



13 ENUR 1

Regulatory gen secrete ADH *(daily rythm – noctural urination)*

Fluid restrictions

Endocrinologic evaluation of hypothalamic dysfunction

Neurometabolic symptoms:

Disorders of behavior
Disorders of thirst
Disorders of appetite
Disorders of temerature regulations
Disorders in circadian rythm

Hormonal symptoms:

- **Deficiency of measurement basal circulatory hormons (cortisol, LH, FSH, GH, TSH).**
- **The secretion of pituitary (tropic-TSH, GH,ACTH,) hormones increase after stimulations adequate hypothalamic neurohormones**: TRH; GHRH; CRH; GnRH
- Diabetes insipidus
- Increased level of PRL

Hypothalamic dysfunction susp.

Hypothalamus damage

MR

- **Tumors** (craniopharyngioma), **metastasizes**
- **ischemic damage, after surgery operation**
- **Inherited disorders**
- **Autoimmune, granulomas histiocytosis,** etc

Hypopituitarism

Hypopituitarism is manifested by diminished or absent of one or more pituitary hormones

- **Gonadotropin** (LH, FSH),
- **Adrenocorticotropin** (ACTH),
- **Thyreotropin** (TSH),
- **Growth Hormone** (GH)
- **Prolactin** (PRL).

Etiology of hypopituitarism:

1. **Inherited disorders**
   - Anatomic malformations (gland, stalk)
   - Incompetence of the diaphragma sellae (empty sella syndrom), hydrocephalus
2. **Tumors**
   - pituitary (cystis, adenomas)
   - pituitary stalk (infundibuloma)
   - hypophysis (craniopharyngioma, germinoma, glioma)
   - metastatic lesions (ca mammae)
3. **Infectious and infiltrative**
   - Tuberculosis, syphilis, myotic infections
   - Sarcoidosis, hemochromatosis, histiocytosis X,
   - immunologic
4. **Injury**
   - Postpatrum hemorrhage (Sheehan syndrome)
   - Hemorrhagic infarction- pituitary apoplexy, ischemic pituitary necrosis
5. **Iatrogenic**
   - Surgical and radiation therapy
6. **Isolated (monotropic)**
   - GH deficiency (ACTH, TSH, PRL - is very rare)
   - LH, FSH deficiency, Gn-RH deficiency – Kallman's syndrome

Onset of pituitary insufficiency Clinical features 1

GH deficiency: in children - short stature, in adults - decreased sence of well-being, lower health-related quality of life, decreased muscle mass, increased fat mass

TSH deficiency: cold intolerance, dry skin, mental dullnes, bradycardia, constipation, anemia (like in primary thyroid failure but clinical changes are less severe and goiter is absent)

Onset of pituitary insufficiency Clinical features 2

- ACTH deficiency: weakness, nausea, vomiting, anorexia, weight loss, fever, hypotension (like in primary adrenal failure)
- PRL deficiency: symptom of PRL deficiency is failure of postpartum lactation
- Gonadotropin deficiency: hypogonadism, oligomenorrhea, amenorrhea in women in men eunochoid apperance

Pituitary insufficiency
Hormonal symptoms:
Deficiency of measurement basal circulatory hormons (cortisol, LH, FSH, GH, TSH)
The secretion of pituitary (tropic- TSH, GH,ACTH,) hormones NOT increase after stimulations adequate hypothalamic neurohormones:
TRH; GHRH; CRH; GnRH

MR

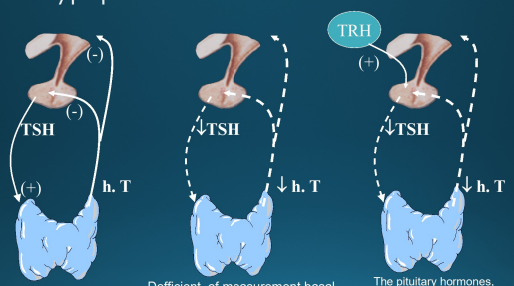
Tumors (craniopharyngioma), **metastasizes**

ischemic damage after surgery operation

Inherited disorders

Autoimmune, granulomas histiocytosis, etc

Hypopituitarism

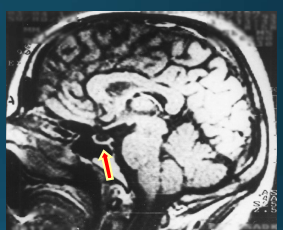


physiology

Defficient of measurement basal circulatory hormons (h.t) in the presence of defficient physiologic pituitary hormones

The pituitary hormones, are not stimulated by adeqate hypothalamic neurohormones (TRH)

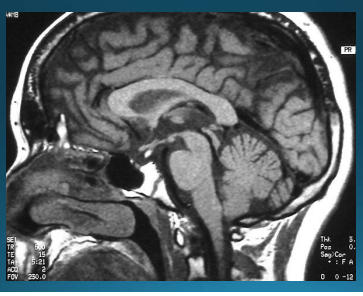
partum
hemorrhage (placenta previa)
- no apetite
- lost of pubic and axillae hairs
- hypotension
- skin cold and dry
- no lactation



Diagnosis:
(Sheehan's syndrome)

M.C. ♂ born. 1975

Aplasia of pituitary



hypopituitarism

Hydrocortison 10-20 mg/d
DHEA 5-10 mg/d

L-Thyroksyn
25 – 100 μg/d

♀ E_2 + P (low doses)
♂ Testost. prol (undec.)
100-200 mg/2 tyg

Acromegaly & gigantism

Acromegaly

The characteristic clinical manifestation are the consequence of chronic GH (pituitary adenomas) hypersecretion which in turn leads to excessive generation of IGF-1 the mediator of the most effects of GH

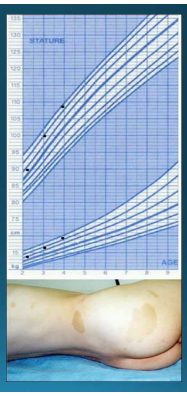
Gigantism

- In childchood and adolescence the onset of chronic GH excess leads to gigantism
- Many of these patients have associated hypogonadism which delays epiphysial closure, and the combination of IGF-1 excess and hypogonadism leads to striking acceleration of linear growth
- most patients also have features of acromegaly if GH hypersecretion persists through adolescence and into adulthood.

Etiologies of Growth Hormone Excess.

Sporadic Growth Hormone Excess		Syndromic/Familial	
Disorder	Pathogenic Mechanism	Disorder	Pathogenic Mechanism
Hypothalamic/ Pituitary GH excess	Congenital GHRH excess (postulated)	Neurofibromatosis-1	Tumor infiltration into somatostatinergic pathways (posulated)
	Pituitary somatotroph or mammosomatotroph adenoma	McCune-Albright syndrome	Activating mutation of Gsa
	Pituitary hyperplasia	Multiple endocrine neoplasia Type-1	Defect in tumor suppression from mutations in menin gene
	Hypothalamic gangliocytoma/ neurocytoma	Carney complex	Abnormality at 2p16 Mutations in PRKAR1A at 17q22-24
Ectopic GH excess	GHRH or GH production by bronchial, carcinoid or pancreatic neoplasm	Familial somatotrophinomas	Mutation in putative tumor suppressor gene at 11q13❖ Abnormality at 2p12-6
	Ectopic pituitary adenoma		

GH-growth hormone, GHRH-growth hormone-releasing hormone, PRKARIA-protein

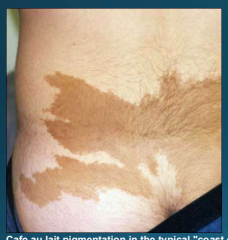


Growth acceleration and characteristic „coast of California" cafe au lait macules
In a child with neurofibromatosis and gigantism

McCune-Albright syndrome (MAS)

MAS is a complex and heterogenous disorder in which GH excess may arise in conjunction with additional endocrinopathies and other abnormalities.
MAS results in the triad of
- precocious puberty,
- café-au-lait skin pigmentation,
- and fibrous dysplasia of bone.

This is a result of activating mutations of Gsa, the stimulatory subunit of the heterotrimeric G-protein complex involved in intracellular signaling.
The incidence of GH excess in classic MAS has generally been reported to be 15-20%. Additional phenotypic features in this subgroup of patients with MAS includes a higher incidence of vision and hearing deficits, TRH responsiveness and hyperprolactinemia.



Cafe au lait pigmentation in the typical "coast of Maine" configuration in an individual with McCune-Albright syndrome.

Multiple Endocrine Neoplasia-Type I (MEN-1)

MEN-1 is one of a number of familial cancer syndromes characterized by autosomal dominant inheritance and multi-endocrine gland involvement. Although significant clinical heterogeneity exists in terms of specific tumor combinations, the most frequent manifestations of MEN-1 are parathyroid, pancreatic and pituitary adenomas.

The gene for MEN-1, which had previously been mapped to chromosomal locus 11q13, has now been cloned and demonstrated to encode for a 610 amino acid nuclear protein designated **menin**.

Anterior pituitary adenomas in individuals with known MEN-1 have a reported prevalence of 10-60%, and are thought to represent the first clinical manifestation of the disease in up to 25% of sporadic cases. GH-secreting adenomas developing in approximately 10% of individuals with MEN-1 by age 40.

Carney Complex (CNC)

1. CNC is a rare autosomal dominant disorder in which the cardinal features include multiple endocrine tumors, skin lentigines (spotty pigmentation), cardiac myxomas and neural sheath tumors.
2. The condition shares characteristics with several other syndromes, including MEN-1 (multiple endocrine tumors), MAS (endocrine hyperfunction and skin pigmentation) and Peutz-Jeghers (mucosal lentiginoses and gonadal tumors). The 50% of patients have a positive family history for the disease.
3. Two distinct genetic abnormalities have been implicated in the pathogenesis of CNC. The first consists of a locus on 2p16, and second mutations in the gene encoding for the protein kinase A regulatory **subunit (1a) (PRKAR1A)** at 17q22-24.

Familial Somatotropinomas

It has been recognized that isolated pituitary gigantism or acromegaly may occur in a familial pattern.

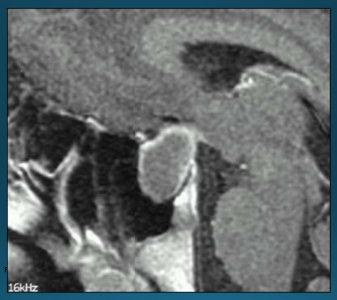
This phenomenon, termed "Isolated Familial Somatotropinomas" (IFS), is defined as the development of GH hypersecretion in two or more members of a family that does not exhibit features of MEN-1 or CNC.

Gigantism *clinical features*

- Rapid increase of height
- Enlargement of the lower jaw
- Enlargement of feet, hand
- Tendency for sweating and acromegalic features

Gigantism - *etiology*

- Hypersecretion of GH (adenoma)
- Hypersecretion of GHRH
- Ectopic production of GHRH



Pituitary somatotroph macroadenoma in an adolescent with gigantism.

Other endocrine and metabolic abnormalities

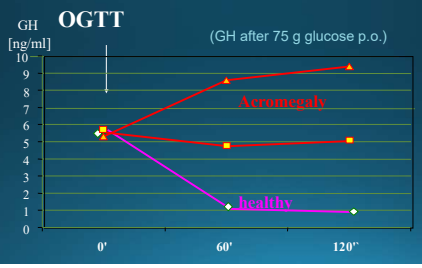
- Hypogonadism
- Hyperprolactinemia
- Hyperinsulinemia
- Glucose intolerance
- Galactorrhea
- Gynecomastia

Gigantism

Diagnostic are similar to those in adults in acromegaly

Diagnosis

Clinical symptoms and sings: acral enlargement, soft tissue proliferation with enlargement of the hands, feet, increasing sweating, heat intolerance, oiliness of the skin, fatique, joint pain, goiter, acanthosis nigricans, photophobia, papillomas, hipertrichosis renal calculi



Diagnosis and treatment

- GH secretion (normal 1-5 ng/ml) are >10 ng/ml to over 500 ng/ml, or in OGTT GH levels do not decrease to less than **1,0 ng/ml (glucose do not inhibits GH secretion)**
- IGF-1 masurement elevated over the normal range for age and sex
- pituitary adenoma MR

Treatment

- Surgical treatment transsphenoidal microsurgery , somatostatin