Introduction to Endocrinology. Diseases of the pituitary and the hypothalamus

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Fields of Endocrinology

- Pituitary (Hypothalamus)
- Thyroid
- Parathyroid
- Adrenal
- Gonads
- Diabetes mellitus
- Multiple endocrine Neoplasia

Causes of hypothalamic dysfunction

- Tumors (astrocytoma, glioma, germinoma, craniopharyngeoma, big pituitary tumors, lymphoma)
- Bleedings
- Developmental abnormalities (arachnoid cysts, holoprosencephaly)
- Granulomatous inflammation (histiocytosis X, sarcoidosis, TBC)
- Inflammation (Encephalitis, Meningitis)
- Trauma
- Irradiation
- Inherited diseases

Diseases of the Hypothalamus

- Lack of trophic hormones (CRH, TRH, GnRH, GHRH) – Growth delay, Hypopituitarism, Disorders of sexual development (isolated GnRH deficiency – Kallmann-syndrome)
- Deficiency of posterior pituitary hormones – diabetes insipidus
- Non-endocrine consequences of hypothalamic disorders:
  - Appetite problems (Anorexia, Hyperphagy, Obesity)
  - Disorders of liquid homeostasis (Adipsia, Polydipsia)
  - Disorders of thermal regulation (Hyperthermia, Hypothermia)
  - Somnolence, Coma
  - Mood problems

Diseases of the pituitary

- Adenomas (Micro-, Macro-, Incidentaloma)
- Anterior pituitary
  - Hormone overproduction (60-70%)
    - Prolactin
    - GH
    - ACTH
    - TSH (very rare)
  - Hormonally inactive pituitary tumors (including gonadotropin-secreting) (30-35%)

  Hypopituitarism
- Posterior pituitary
  - Diabetes insipidus
  - SIADH

Micro- and Macroadenoma

- Limit: 10 mm
- Consequences:
  - Hormone overproduction
  - Mass Effects
    - Visual field disturbance
    - Hormone deficiencies (1. GH, 2. LH/FSH, 3. TSH, 4. ACTH)
    - Increased prolactin (Stalk lesion)
    - Intracranial hypertension
    - Neurological complications
- Mostly benign, pituitary carcinoma is extremely rare, only in case of metastases (intracerebral, craniospinal)

Epidemiology of pituitary adenomas

Pituitary adenomas are the most frequent intracranial tumors – Prevalence: 77/100.000

- **1. Prolactinoma**
- **2. Hormonally inactive (including Gonadotropin secretion without clinical consequences)**
- **3. GH, much rarer**
- **4. PRL + GH**
- **5. Cushing-disease**
- **6. TSH (Inzidence: 1-2/10 Million/Y)**

Investigating pituitary adenomas

- Hormonal examinations - Screening
  - Prolactin
  - Cortisol, ACTH
  - TSH, fT4
  - IGF-1
  - LH, FSH, Sexual steroids
- Imaging (MRI)
- Ophtalmological examination

Treatment of pituitary adenomas

- Surgery – Macroadenomas, Visual sight defects, neurological complications, liquorrhoea, hormone overproduction (except prolactinomas)
- Medicamental treatment (Prolactinoma, Acromegaly)
- Irradiation therapy (gamma-knife)

Prolactinoma

- The most common form of pituitary adenoma
- Microprolactinoma vs. macroprolaktinoma (Limit 10 mm)
- Prevalence 44/100.000
- Typical symptoms in women, often without symptoms in men

Symptoms of prolactinoma

Women

- Galaktorrhoea
- Amenorrhoea/ Raromenorrhoea
- Osteoporosis

Men

- Loss of libido
- Impotence
- Osteoporosis

- **Mass effects in both**
- Visual field defects
- Hormone deficiency
- Neurological complications

Normal Prolactin levels

- Normal range: 5-20 ng/ml
- Prolactin results in prolactinoma are usually >200 ng/ml.
- In macroprolaktinomas PRL is usually >1000 ng/ml.
- Hook-Effect – in case of very high PRL, lab measurement can be false negative
- Macroprolactin – Polymers of prolactin – non-functional, false positive results – PEG-Reaction to exclude it

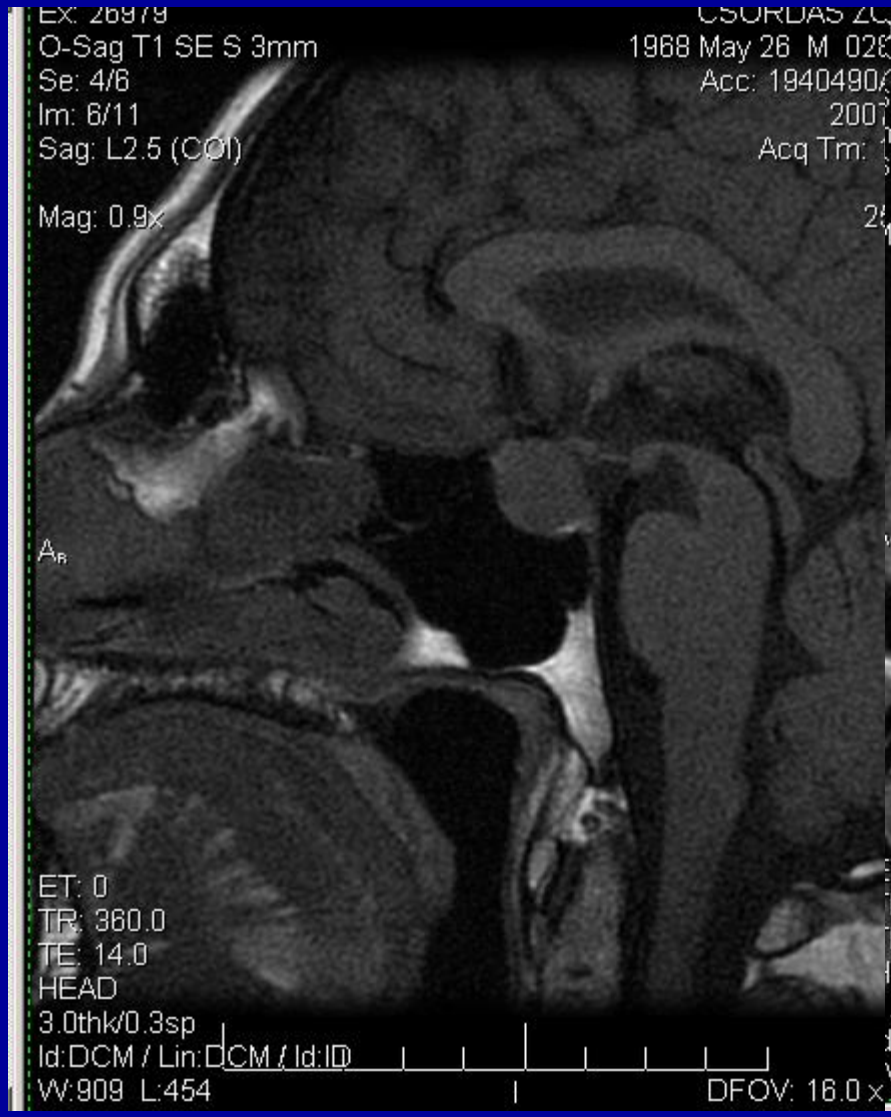
Hyperprolactinemia due to other causes

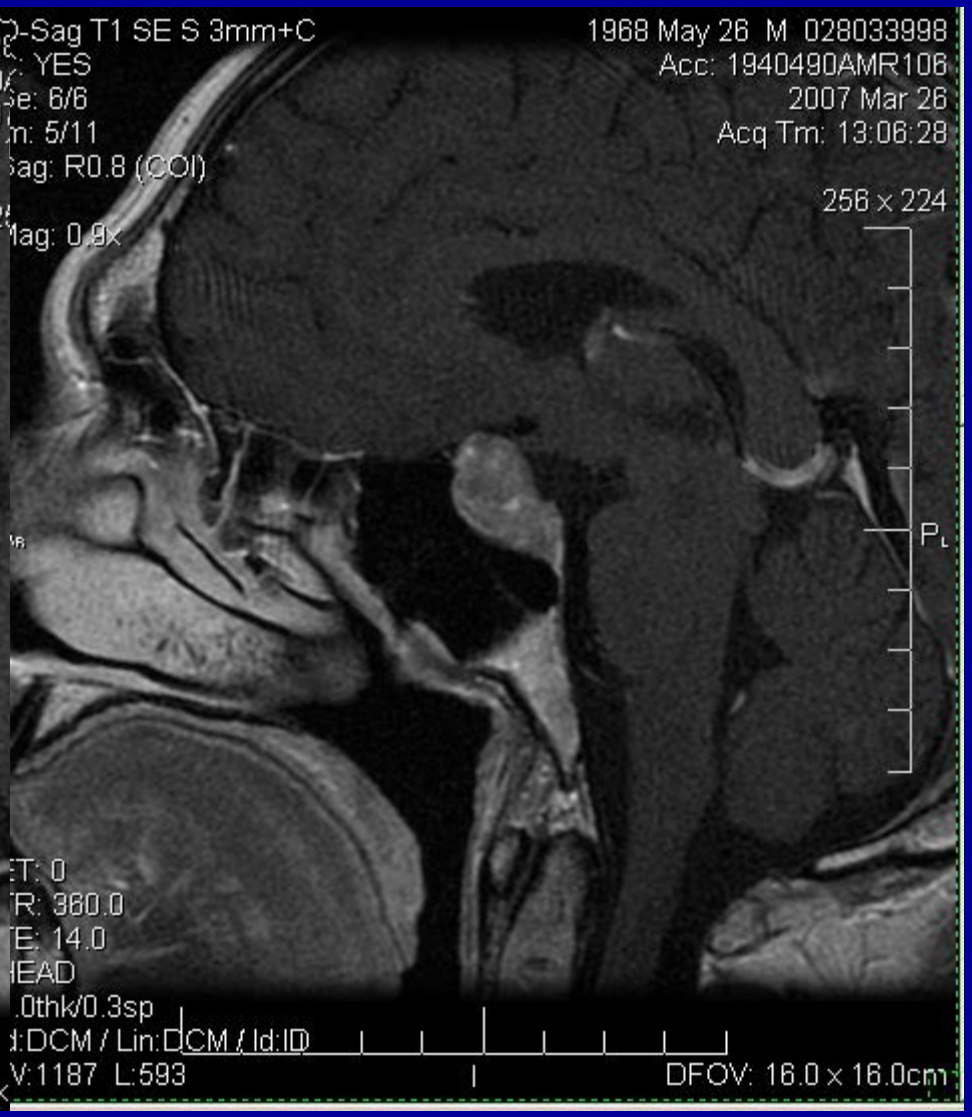
- **Drugs**
- **Pituitary stalk lesion (Trauma, Surgery, Big tumors (Macroadenoa), infiltrative lesions /e.g. sarcoidosis/)**
- **estrogen**
- **hypothyroidism**
- **Chest wall trauma**
- **Chronic renal insufficiency**

Drug causes of hyperprolactinemia

- Dopamin-antagonist drugs (D2-Receptor Antagonists)
- Antipsychotic Drugs – Risperidone
- Antidepressants
- Antiemetic drugs – e.g. Metoclopramide
- Antihypertensive Drugs (Verapamil, Reserpine, Methyldopa)

Macroprolaktinoma





Therapy of Prolactinoma

- **Drug Therapy – Dopamin Agonists**
  - **Bromocriptin – Ergot-Derivative**
  - **Quinagolid**
  - **Cabergolin - Ergot-Derivative**

Surgery – threatining visual field loss, neurological consequences, ineffective drug treatment, lack of compliance

Irradiation therapy

A case

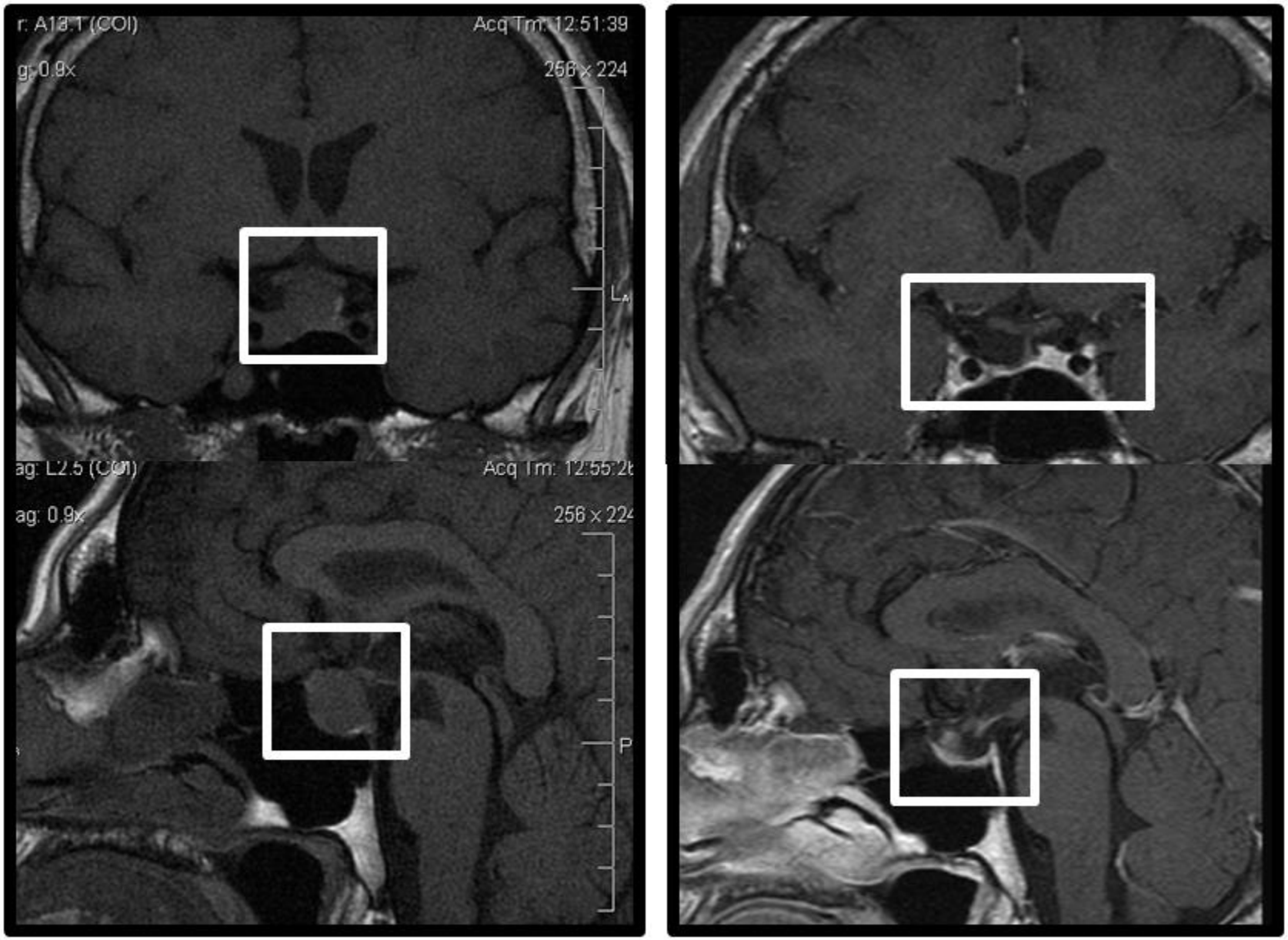
- 42 year old man, complains of libido loss
- No urological cause, but testosterone level very low
- Prolaktin level 1472 ng/ml (norm. <10)
- Macroprolaktin: 247 ng/ml
- Sella MRI - Macroadenoma
- No chiasma lesion, Bromocriptin started

Before Bromocriptin

4 Years after Bromocriptin

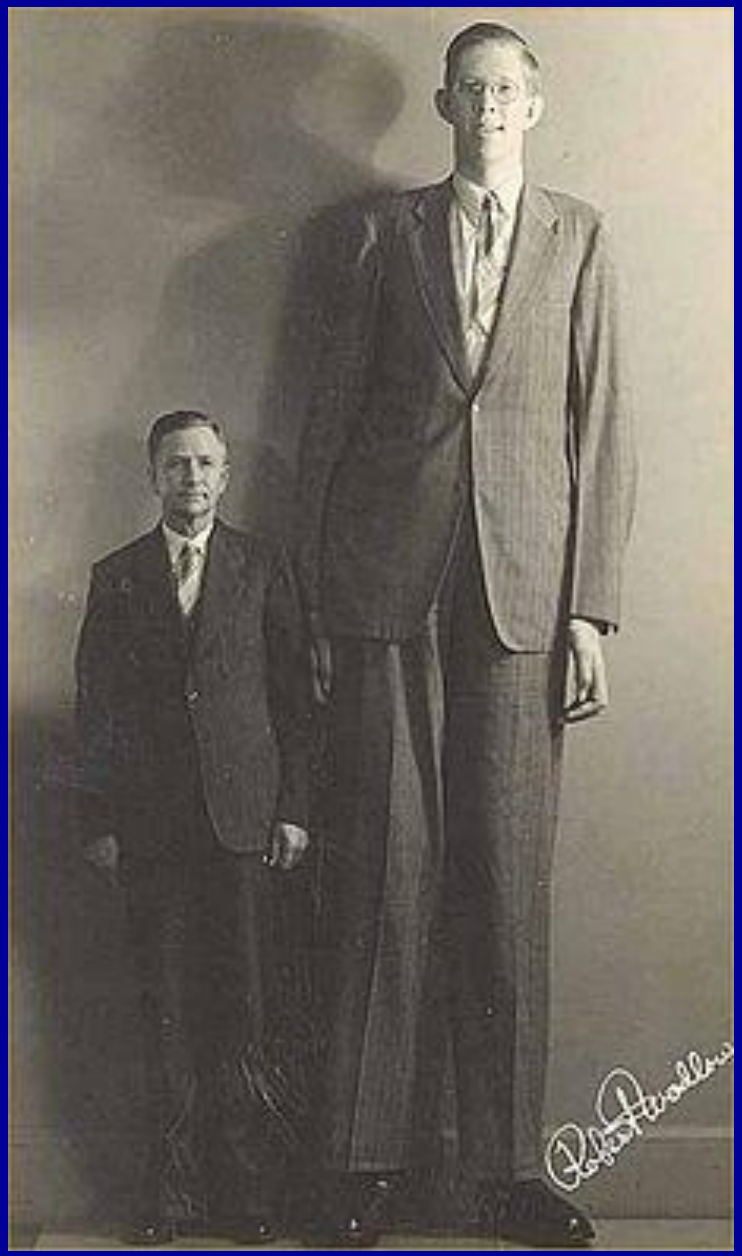
Frontalis

Sagittalis



Akromegaly and Gigantism

Rare disease
Prevalence: 30-70/Million

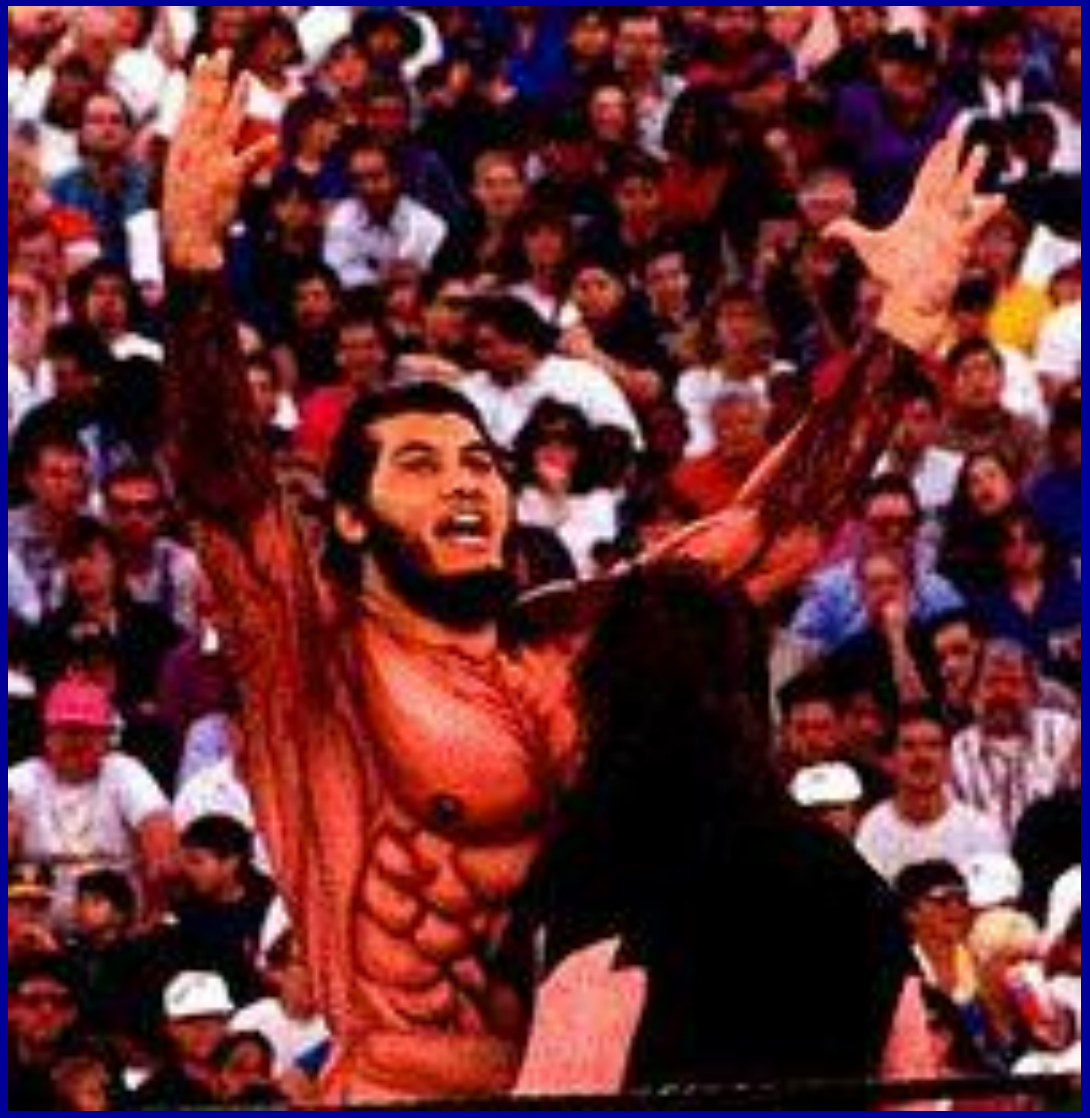


Robert Wadlow
The tallest man of the world
2.72 m

Wikipedia

Anna Swan
2.27 m
With her parents

Wikipedia



Giant Gonzalez
2.29 M

Wikipedia

Maurice Tillet and Shrek

Wikipedia

Symptoms of acromegaly

- Growth of the „Acras”: Hands (Sausage fingers), feet, nose, tongue (makroglossia), ears, lips, carpal tunnel syndrome
- Glove size? Shoe size?
- Visceromegaly (Cardiomegaly) – Hypertension, Heart insufficiency, Sleep apnea
- Increased tumor prevalence – Colon polyposis, Colorectal Cc.
- Sweating
- Diabetes mellitus
- Endocrine disorders (Raromenorrhoea, Impotence)

Death causes in acromegaly

- Cardiovascular (Heart insufficiency) 60%
- Respiratory (25 %)
- Cancer (15%)

Laboratory diagnosis of Acromegaly

- Screening – Serum IGF-1
- Confirmation - OGTT (Oral glucose tolerance test) – 75 g Glucose per os, Blood taking 0’, 30’, 60’, 90’, 120’, 180’
- Normally GH goes below 1 ng/ml, in case of acromeagly it does not go below 2 ng/ml, often a paradoxical increse of GH is observed

Treatment of acromegaly

- 1. Surgery
  - Success rate for microadenomas: 70-90%
  - Success rate for macroadenomas: 50-70%
- 2. Drug Therapy
  - Somatostatin Analogues (Octreotide, Lanreotide, Pasireotide)
  - GH-Receptor Antagonist, Pegvisomant (Somavert)
  - Dopamine Agonists (Cabergolin)
- 3. Irradiation

A case of acromegaly

- The new GP of a 41 Y old man noticed the typical face changes. He had a history of insulin-treated diabetes mellitus for 3 years.
- IGF-1 942 (strongly increased), paradoxal increase during OGTT
- Sella MRI showed a pituitary macroadenoma
- Operation via paraseptal-transsphenoidal route
- Postop. OGTT: no supression – Op. unsuccessful

Case of acromegaly 2.

- Somatostatin Analogue, Octreotide LAR started, IGF-1 reduced, but not normalized
- MRI control shows a residual tumor (recurrence), reoperation
- Postop. OGTT: again no supression
- Octreotide LAR than, Lanreotide, IGF-1 not normalized
- Pasireotid LAR started, then IGF-1 became normal. Insulin doses had to be increased.

- **Primary insufficiency**
  - Disease of the peripherial hormone producing organ (thyroid, adrenal cortex, gonads)
  - peripherial hormone low, pituitary hormone increased
- **Secondary insufficiency**
  - Lack of the pituitary front lobe hormones
  - Peripherial hormone low, pituitary hormone low
- **Tertiary insufficiency**
  - Lack of hypothalamic trophormones, all hormone levels are low

Hypopituitarism
Pituitary anterior lobe insufficiency

- Loss of one or more anterior lobe hormones
- Prevalence 46/100.000, Incidence: 4/100.000/Y
- Order of the loss of anterior lobe hormones:
  - 1. GH
  - 2. LH/FSH
  - 3. TSH
  - 4. ACTH

Causes of Hypopituitarism

- Neoplastic – pituitary/sellar or hypothalamic tumors
- Traumatic – Operation, Trauma, Irradiation
- Congenital – e.g. Prader-Willi sy, Laurence-Moon-Biedl sy, Kallmann sy
- Inflammatory – autoimmune hypophysitis, TBC, Syphilis, Meningoencephalitis
- Infiltrative - Sarcoidosis, Histiozytosis X, Hämochromatosis
- Vascular – postpartal necrosis (Sheehan-syndrome), Carotis-aneurysm, cavernous sinus thrombosis, stroke
- Drug-induced (long steroid therapy)

Sheehan-Syndrome

- Pituitary infarction in the peripartal period
- Milder Case – Mangel von Muttermilch, Prolaktinverlust, dann weitere Symptome des Hypopituitarismus, Verlust von Sexualbehaarung, Amenorrhö bleibt nach der Geburt
- Schwieriger Fall – Anorexie, Gewichtsverlust, Lethargie

Symptoms

- Weight loss, fatigue, weakness, fine wrinkles on the face, hypotension
- Secondary hypogonadism – loss of libido, secondary amenorrhea, impotence
- Secondary hypothyroidism – cold intolerance, bradycardy, obstipation, hyponatremia
- Secondary adrenal insufficiency – hypotension, weakness, paleness, malaise, hyponatremia
- No aldosterone deficiency – NO hyperkalemia
- Prolactin deficiency – Inability to lactate (Stalk lesion leads to mildly increased prolactin)
- GH-deficiency in adults – Fatigue, muscle loss, increased fat

GH-Deficiency

- **In children**
  - **Proportional dwarfism**
- **In adults**
  - **Change in body composition– increased fat**
  - **Reduced muscle amount**
  - **Reduced life quality**
  - **Dyslipidemia**
  - **Cardiovascular risk factors**

Wikipedia

Wikipedia

Hormonal Diagnosis

- **LH, FSH low – Testosterone, estradiol (E2) low - secondary hypogonadism**

(In contrast, in primary hypogonadism, LH, FSH are high)

- **IGF-1 low – GH-deficiency**
- **TSH low, fT4 low (in primary hypothyroidism, TSH is high)**
- **ACTH low, cortisol low (in M. Addison, ACTH is high) – if cortisol is >20 ug/dl (540 nmol/l) in the morning, adrenal insufficiency is excluded**
- **Synacthen-test – 250 ug Tetracosactid, 60' later Kortizol > 20 ug/dl (540 nmol/l) – *the adrenal cortex atrophises in ACTH-deficiency***

Dynamic Tests in the diagnosis of hypothalamus-pituitary diseases

- TRH-Stimulation
- LHRH-Stimulation
- Insulin-Hypoglycemia

Insulin-Hypoglycemia Test

- Hypoglycemia provokes ACTH and GH
- 0.1-0.15 E/Kg rapid acting insulin i.v.
- Blood taken every 15 Min. after insulin and during hypoglycemia (blood sugar <2.2 mmol/l)
- GH deficiency:
  - GH < 3 ng/ml in adults
  - GH < 7 ng/ml in children

Therapy 1.

- **Glucocorticoid substitution**
  - Hydrocortison – 15-20 mg/D – highest dose in the morning
  - Prednisolon 5 mg/D
  - Strong increase in acute cases (e.g. 3x100 mg Hydrocortison/D intravenously in shock, surgery)
- **L-Thyroxine**
  - 1.6-1.8 µg/kg/D – in general 100-150 µg/D - **monitoring fT4**

ALWAYS GLUCOCORTICOIDS FIRST, THEN L-THYROXINE

Therapy 2.

- Substitution with sex hormones
  - 1. Development and maintenance of secondary sex characteristics
    - Testosterone – Injection, Transdermal
    - Estrogen substitution
  - 2. Development of fertility
    - LH/FSH Substitution, β-HCG
- GH-Substitution
  - Daily GH administration, approx. 1 IU/D (monitor with IGF-1)

DIABETES INSIPIDUS

Main forms of Diabetes insipidus

- Central Diabetes insipidus.
- Nephrogenic diabetes insipidus.
- Transient Diabetes insipidus during pregnancy (due to increased ADH metabolism)
- „Primary Polydipsia” – mostly in psychiatric diseases or bad habit, the most important differential diagnostic issue

Main causes of central Diabetes insipidus

- Not frequent, incidence: 4/100.000 Person/Y
- Main causes:
  - Trauma
  - Neurosurgery (for a pituitary tumor)
  - Tumors of the hypothalamus and pituitary
  - Rare inflammatory diseases (Histiocytosis X, Sarcoidosis)
  - Intracranial bleeding, Sheehan Syndrom
  - Very rare congenital forms

Main symptoms and diagnosis of Diabetes insipidus

- Polyuria, variable, can reach 18-20 Liter per day in the most severe forms.
- Polydipsia.
- Low urine density(1001-1005 g/cm^3) and Osmolality (<200 mosmol/kg).
- Thirst probe: the patient cannot concentrate the urine – danger of exsiccosis
- Oral Water and Salt administration (20 ml/kg water and 0.9 % NaCl for 2 days): in healthy people, the diuresis after NaCl is lower than after water.
- Differential diagnosis between central and nephrogenic DI: administration of desmopressin leads to reduction of urine production in central DI

Treatment of central DI

- ADH is not stable enough for clinical use
- ADH-analogue Desmopressin, DDAVP mostly as nasal spray, also available as tablets
- Daily dose: 1-2x 1 Spray, or 3x100-200 µg in tablets.

Nephrogenic DI

- Problem of the renal effect of ADH
- Two main forms:
  - Rare congenital forms (VP2 or AQP2 mutations)
  - Acquired forms (chronic renal diseases, metabolic disorders /hypercalcemia, hypokalemia, gout/, osmotic diuretics /mannitol/, drugs /lithium, demeclocyclin, vincristin/)
- Treatment:
  - NSAID (Indomethacin, Ibuprofen, Aspirin) reduces the polyuria, increases osmolality
  - mild volume depletion, thiazides in combination with NSAID. K-sparing diuretics (amilorid) + thiazides is also effective.