Disorders of the anterior pituitary and hypothalamus

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1. Introduction
2. Pituitary anatomy/development
3. Physiology of adenohypophyseal hormones
4. Hypopituitarism (inherited/acquired)
5. Pituitary tumors, other sellar masses
6. Specific hormone producing tumors:
   - Prolactinoma
   - Acromegaly
   - Cushing disease
Introduction

- The pituitary often referred to as „master gland” because together with the hypothalamus, it orchestrates the complex regulatory functions of multiple endocrine glands.
- ~ consists of anterior and posterior lobe.
- Anterior ~ produces six major hormones: PRL, GH, ACTH, LH, FSH, TSH
- Pituitary hormones are produced in pulsatile manner.
Introduction

- Each pituitary hormones elicits specific responses in peripheral target tissues.
- The peripheral glands hormones, in turn, exert feedback control at the level of the hypothalamus and pituitary to modulate pituitary function.
Introduction

- Pituitary tumors cause characteristic hormone excess syndromes.
- Hormone deficiency may be inherited or acquired.
- Efficacious treatments exist for the various pituitary hormone excess and deficiency syndromes.
- Nonetheless, these diagnoses are often elusive.
The pituitary gland located within the sella turcica ventral to the diaphragma sellae.

The sella is contiguous to vascular and neurologic structures:
- Cavernous sinus
- Cranial nerves
- Optic chiasm
Expanding intrasellar pathologic processes may have significant central mass effects in addition to their endocrinologic impact.
Anatomy

- Hypothalamic neural cells synthesize specific releasing and inhibiting hormones that are secreted directly into the portal vessels of the pituitary stalk.
- This portal plexus allows reliable transmission of hypothalamic peptide pulses, without systemic dilution.
Pituitary development

- Adenohypophysis is formed from an evagination of the primitive roof of foregut (Rathke’s pouch)
- Neurohypophysis an evagination from the floor of the diencephalon
- Adenohypophysis – endocrin gland
- Neurohypophysis is part of the brain
Hypothalamic – pituitary function

- Hypothalamic peptides are produced in pulsatile manner → consequently pituitary cells are exposed to sharp spikes of releasing factors and in turn release their hormones as discreted pulses.
Anterior pituitary hormones

- Prolactin (PRL)
- Growth hormone (GH)
- Adrenocorticotropicin (ACTH)
- Gonadotropins (FSH, LH)
- Thyreotrop hormone (TSH)
Prolactin

- Consist of 198 aminoacid
- Weekly homologous to GH and hPL
- Prolactin is synthetised in lactotropes (20% of anterior pituitary cells)
- Lactotropes and somatotropes are derived from a common precursor cell.
- Marked lactotrope cell hyperplasia develops during the last two trimester of pregnancy and the first few months of lactation.
- Normal serum level 10-20 µg/l, pulsatile → peak serum level: 4 – 6 a.m.
Prolactin

- Unique → central control mechanism is inhibitory!
- Dopamine supress PRL release
- PRL hypersecretion occurs after pituitary stalk section
- D₂ receptor mediate PRL inhibition
- TRH → PRL ↑ within 15-30 min of iv. inj.
- VIP → PRL ↑
- TSH, glucocorticoids → PRL ↓
- PRL ↑: exercise, meals, sexual ic, acute stress, minor surgical procedures, AMI...
Prolactin

- During pregnancy ~ 10x ↑
- In breast, lobuloalveolar epithelium ↑
- Induce and maintain lactation
- Decrease reproductive function → hypothalamic GnRH ↓
- Suppress sexual drive
Growth hormone

- The most abundant pituitary hormone
- Somatotrope cells constitute 50% of ant. pituitary cell population
- Controlled by complex hypothalamic and peripheral factors:
  - GHRH → GH ↑
  - Ghrelin → GH ↑
  - Somatostatin → GH ↓
  - IGF-1 → GH ↓
  - Glucocorticoids → GH ↓
Growth hormone

- Secretion is pulsatile, greatest level at night
- GH ↑: deep sleep onset, after exercise, physical stress, trauma, sepsis
- GH ↑: chronic malnutrition, prolonged fasting, high protein meals (L-arginine)
- Protein synthesis ↑ (muscle mass ↑)
- Impaires glucose tolerance (gluconeogenesis ↑)
- Lipolysis ↑
- Na, K, Ca, P and water retention
- Linear bone growth
- Stimulates IGF-1 secretion (growth int. organs ↑)
Corticotrope cells constitute 20% of pituitary cells

Derived from POMC precursor protein

ACTH↑: CRH, arginin vasopressin, proinflamatory cytokines (IL-6)

ACTH↓: glucocorticoids

ACTH secretion is pulsatile → circadian rythm
  - Peak: 6 am, nadir: midnight

Glucocorticoids follows paralell diurnal rythm
Gonadotropin hormones

- Gonadotrop cells comprise of 10% of anterior pituitary cells
- Produce: FSH, LH
- Dynamically regulated
- Hypothalamic GnRH regulates the synthesis and secretion
Thyreotrop hormone

- Thyreotrop cells comprise ~ 5% of AP cell population
- Structurally related to FSH, LH
- TRH (hypothalamic tripeptide) → TSH ↑
- Thyroid hormones, dopamine, glucocorticoids → TSH ↓
- Long standing hypothyreoidism → TSH ↑
- TSH:
  - Thyroid follicle ↑
  - T3, T4 ↑
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   - Acromegaly
   - Cushing disease
Hypothalamic and anterior pituitary insufficiency

- Hypopituitarism results from impaired production of one or more anterior pituitary tropic hormones.

- Inherited disorders
- Acquired
Inherited pituitary dysfunction

- **Kallmann syndrome** – GnRH defect, anosmia, olfactory agenesis
- **Laurence-Moon-Biedl syndrome** – obesity, central DI, hexadactily, blindness
- **Fröhlich syndrome** – hyperphagia, obesity
- **Prader-Willi syndrome** – extrem obesity + muscle hypotonia
Aquired pituitary dysfunction

1. Hypothalamic infiltration disorders
2. Inflammatory lesions
3. Cranial irradiation
4. Lymphocytic hypophysitis
5. Pituitary apoplexy
6. Empty sella
7. Pituitary tumors
Hypothalamic infiltration disorders

- Sarcoidosis
- Histiocytosis X
- Amyloidosis
- Haemochromatosis
Inflammatory lesions

- TBC
- Opportunistic fungal (Histoplasmosis, Pneumocystis jiroveci) or parasitic (Toxoplasmosis) infections associated with AIDS
- Tertiary syphilis
- Bacterial meningitis
- Abscess
Cranial irradiation

- Head and neck tumors
- Pituitary or sella masses treatment
Lymphocytic hypophysitis

- Pregnant or post-partum women
- MRI shows prominent pituitary mass resembling an adenoma
- Pituitary failure – diffuse lymphocyte infiltration
- Autoimmune? (Associated with Hashimoto-thyroiditis, pernicious anaemia etc.)
- Respond to glucocorticoid treatment
Pituitary apoplexy

- Spontaneously in preexisting adenoma
- Postpartum – Sheehan’s sy.
- DM, HT, sickle cell anaemia, acute shock

Endocrine emergency:
- Severe hypoglycemia
- Hypotension
- CNS hemorrhage
- Death

Acute symptoms:
- Severe headache
- Meningeal irritation
- Bilateral visual changes
- Ophthalmoplegia
- Cardiovascular collapse

Pituitary CT
Therapy: high-dose glucocorticoid
Surgical decompression
Empty sella

- Often incidental MRI finding
- These patient often has normal pituitary function
- Hypopituitarism can develop incidiously
- Pituitary mass can undergo clinically silent infarction
# Clinical presentation of hypopituitarism

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Sign and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH</td>
<td>Growth disorders, abnormal body composition, energy ↓, mental function ↓, CVD ↑</td>
</tr>
<tr>
<td>FSH,LH</td>
<td>Menstrual disorders, infertility, loss of secondary sexual characteristic</td>
</tr>
<tr>
<td>TSH</td>
<td>Hypothyreodism</td>
</tr>
<tr>
<td>ACTH</td>
<td>„White Addison disease“</td>
</tr>
<tr>
<td>PRL</td>
<td>Failure of lactation</td>
</tr>
</tbody>
</table>

**Hypopituitarism**

This man has loss of secondary sexual characteristics and absence of pubic hair

**Hypopituitarism**

The patient may complain of feeling cold, lethargic, dizzy on standing, constipation, weakness
### Lab investigation – *stimulation tests*

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH</td>
<td>- Insulin tolerance test</td>
</tr>
<tr>
<td></td>
<td>- GHRH test</td>
</tr>
<tr>
<td></td>
<td>- L-Arginine test</td>
</tr>
<tr>
<td></td>
<td>- L-dopa test</td>
</tr>
<tr>
<td>Prolactine</td>
<td>- TRH</td>
</tr>
<tr>
<td>ACTH</td>
<td>- Insulin tolerance test</td>
</tr>
<tr>
<td></td>
<td>- CRH</td>
</tr>
<tr>
<td></td>
<td>- Synthetic ACTH (Cortrosyn)</td>
</tr>
<tr>
<td>TSH</td>
<td>- TRH</td>
</tr>
<tr>
<td></td>
<td>- Basal thyroid function test</td>
</tr>
<tr>
<td>LH, FSH</td>
<td>- LH, FSH, testosterone, estrogen</td>
</tr>
<tr>
<td></td>
<td>- GnRH test</td>
</tr>
</tbody>
</table>
Treatment of hypopituitarism

- **Hormone replacement therapy**
  - Glucocorticoids
  - Thyroid hormone
  - Sex steroids
  - GH
  - vasopressin
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   - Acromegaly
   - Cushing disease
Pituitary tumors and other sellular masses

- Pituitary tumors
  - Classification of pituitary tumors
- Other sellar masses
- Clinical presentation
  - Local compression symptoms
  - Hormon overproduction
Pituitary tumors

- Pituitary adenomas are the most common cause of pituitary hormone hypersecretion and hyposcretion.
- ~15% of all intracranial neoplasms
- ~25% of normal individuals has small pituitary lesions
- Benign adenomas – monoclonal origin
- Hormonally active tumors → autonomous hormone secretion (diminished responsiveness to inhibition)
- Hormone production may not correlate with tumor size
Classification of pituitary tumors

- **Size**: microadenomas (<1 cm), macroadenomas (>1 cm)

- **Staining**: acidophil, basophil, chromophobe

- **Functional**
  - Hormonally active
  - Hormonally inactive (0 cells, oncocytomas)
Other sellar masses

- Craniopharyngeoma
- Rathke’s cysts
- Sella chordomas
- Meningeomas
- Pituitary metastases ~ 3% cancer patients (50% breast cancer) → Diabetes insipidus
- Hypothalamic hamartomas, gangliocytomas
- Brain germ-cell tumors
Local compression symptoms

- Clinical manifestation depends on anatomic localisation of the mass and direction of its extension.
- **Headache** – stretch the dural plate
- **Visual loss** – bitemporal homonim hemianopia
- Diplopia, ptosis, ophtalmoplegia, facial sensation ↓
- Erosion through sellar floor → liquororrhoea
- Temporal and frontal lobe disorders
- Hypothalamic syndromes
Treatment

- **Transphenoidal surgery**
  - DI, hypopituitarism ~ 20%

- **Radiation**

- **Medical**
  - PRL – dopamin agonists
  - GH, TSH – somatostatin
  - ACTH, non-functioning - Ø
Lecture sketch

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Hyperprolactinaemia

- Hyperprolactinamia is the state of increased serum prolactin.

- Caused by:
  - Dopamin secretion ↓ in hypothalamus
  - Pituitary stalk damage
  - Lactotrop cell function ↑
  - „Autonomic” prolactin producing adenoma
Hyperprolactinaemia – Clinical presentation

- Oligo/amenorrhoea – 90-95%
- Galactorrhoea – 80%
- Infertility

- Impotency
- Infertility

The clinical symptoms does not correlate with serum prolactin level!
Hyperprolactinaemia – Clinical presentation

If the disorder is longstanding

- Osteoporosis
- Loss of libido
- weight ↑
- hirsutism

♀
- Gynecomastia
- Reduced muscle mass
- Decreased beard growth

♂
Hyperprolactinaemia - etiology

1.) Pituitary adenoma
   - Prolactinoma
   - Acromegaly
   - Cushing disease, Nelson-syndrome
Hyperprolactinaemia - etiology

2.) Physiologic hypersecretion

- Pregnancy
- Lactation
- Nipple stimulation and sexual orgasm
- Chest wall stimulation (surgery, herpes zooster)
- Sleep
- Stress
Hyperprolactinaemia - etiology

3.) Hypothalamic – pituitary stalk damage
   - Tumors
   - Empty cella
   - Lymphocytic hypophysitis
   - Adenoma with stalk compression
   - Granulomas
   - Rathke’s cyst
   - Irradiation
   - Trauma
Hyperprolactinaemia - etiology

4.) Systemic disorders
- Chronic renal failure
- Primary hypothyreodism
- PCO syndrome
- Cirrhosis
Hyperprolactinaemia - etiology

5.) Drug-induced hypersecretion

- Dopamine receptor blockers (Phenothiazines, butyrophenones, metoclopramide)
- Dopamine synthesis inhibitors (α-methyldopa)
- Catecholamin depletors (reserpine)
- Opiates (cocaine, morphine, methadone, heroin)
- $H_2$ antagonists (cimetidine, ranitidine)
- Imipramines (amitryptiline, amoxapine)
- Serotonin-reuptake inhibitors (fluoxetin)
- Calcium channel blockers (verapamil)
- Hormones (Estrogens, Antiandrogens, TRH)
Diagnosis – Laboratory investigation

- Basal, fasting morning PRL levels (normally < 20µg/L)
- Pulsatile – several different occasion

<table>
<thead>
<tr>
<th>Physologic states</th>
<th>µg/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>10-20</td>
</tr>
<tr>
<td>Sleeping</td>
<td>&lt;50</td>
</tr>
<tr>
<td>III.d trimester</td>
<td>&lt;300</td>
</tr>
</tbody>
</table>
Hyperprolactinaemia - Diagnosis

1st step: **exclusion** of the following:

- Physiologic hypersecretion
- Drug-induced hypersecretion
- Primary hypothyreodism – TSH, T3, T4
Hyperprolactinaemia - Diagnosis

2nd step

- CT, MRI
- Ophthalmologist
- Pituitary function tests
Hyperprolactinaemia - Treatment

- Drug – withdrawn
- Hypothyreosis – L-thyroxin
- Tumor – resection of hypothalamic or sellar mass
- Granulomatosus – glucocorticoid treatment
- 30% of patient – with or without visible pituitary adenoma resolves spontaneously.
Prolactinoma
Prolactinoma

- 50% of pituitary tumors
- Incidence ~ 3/100,000
- Prevalence ~ 1.5%
- Mixed tumors: PRL/GH, PRL/ACTH, PRL/TSH
- Microadenomas < 1 cm
- Macroadenomas > 1 cm – locally invasive
- Microadenomas ♀:♂ ~ 20:1
- Macroadenomas ♀:♂ ~ 1:1
- 5% microadenoma → macroadenoma
<table>
<thead>
<tr>
<th>Pathologic state</th>
<th>µg/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microprolactinoma</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Macroprolactinoma</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Stalk compression</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Drugs</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>
Treatment of prolactinoma

- **Medical** – dopamine agonist – supress PRL secretion, synthesis and lactotrope cell proliferation
  - Ergot alkaloid – **bromocriptine** – short acting ~ 2.5mg tid
  - Ergoline derivate – **carbegoline** – long acting ~ 1-2/week
  - Side effects: constipation, nausea, vomiting, insomnia, nightmares, vertigo

- **Surgery** - indications:
  - Dopamine resistance or intolerance
  - Invasive macroadenoma
  - Patient request
Acromegaly

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Acromegaly

- GH hypersecretion is usually the result of somatotrope adenoma.
- Other rare reasons (<1%): GHRH producing tumors (small cell lung cancer, medullary thyroid carcinoma, pancreatic islet cell tumor etc.)
- Incidence ~ 3-4/1.000.000/year
- Prevalence 50-70/1.000.000/year
- Females > Males
- Any age can occur, mean age: 40-50 years.
- Macroadenoma ~ 70-75%
- Micoadenomas ~ 25-30%
- Incidious onset, 1st symptom → dg. ~ 7-12 years
- Progressive form – more common among young adults
Acromegaly – clinical presentation

- Acral bony overgrowth
  - Increased foot and hand size – increased shoe/glove size, ring tightening
  - Proximal muscle weakness
  - Carpal tunel sy.

- Face
  - Frontal bossing
  - Large fleshy nose
  - Thicker mouth
  - Course facial features
  - Macroglossia
  - Widened space between the lower incisor teeth
  - Mandibular enlargement – prognathism
  - Oily skin
  - Hyperhydrosis
  - Deep, hollow-sounding voice

- Generalized organomegaly
  - Cardiomegaly, liver and spleen enlargement.
Acromegaly – clinical presentation

- Overall mortality ↑ → survival is reduced by 10 years compared with an age-match control population
- Cardiovascular system
  - Coronary heart disease
  - Cardiomyopathy with arrhythmias
  - Left ventricular hypertrophy
  - Diastolic function ↓
  - Hypertension
- Glucose-intolerance – Diabetes mellitus
- Increased risk for colon polyps → colon tumors!!
- Upper airway obstruction – thyroid gland ↑, tongue ↑
Acromegaly – Laboratory investigation

- Random GH level useless (pulsatile secretion)
- Age and gender-matched IGF-1 levels ↑
- OGTT – failure of GH supression (<1 µg)
- Paradox GH ↑ after glucose or TRH administration
- PRL levels should be measured (↑ in 25%)
- Pituitary hormone tests
Acromegaly – treatment

- **Surgical resection**
  - Initial treatment for most patients
  - Transsphenoidal surgical resection, cure rate ~ 70%
  - GH levels return to normal within 1 hour
  - Hypopituitarism develops 15% of patients

- **Medical treatment**
  - Somatostatin analogues – Octreotide subcutaneously
    - Lanreotide – depot formulation, 4 weeks
  - Dopamine agonists

- **Radiation therapy**
  - Not respond to surgical or medical treatment
  - Stereotactastic ablation by gamma-knife is promising
Cushing syndrome
Cushing syndrome - Cushing disease

- **Cushing syndrome**: combination of symptoms and signs which results from elevation of circulating glucocorticoid levels.

- **Cushing disease**: excessive ACTH production by the pituitary. → Most common cause of endogenous Cushing’s syndrome.
Cushing syndrome

- 70% Cushing disease
- 30% benign or malignant adrenal tumor
- Ectopic ACTH production (small cell lung cancer)
- Iatrogenic hypercortisolism is the most common cause of cushingoid features!
Cushing disease

- ACTH producing pituitary tumor
- Incidence 2.4/1,000,000/year
- Prevalance 39/1,000,000/year
- $\text{♀:♂} = 5-10:1$
- 10-15% of all pituitary tumors
- Microadenomas
- They retain partial suppressibility in the presence of high doses glucocorticoids
Cushing disease

- Emotional disturbance
- Enlarged sella turcica
- Moon facies
- Osteoporosis
- Cardiac hypertrophy (hypertension)
- Buffalo hump
- Obesity
- Adrenal tumor or hyperplasia
- Thin, wrinkled skin
- Abdominal striae
- Amenorrhea
- Muscle weakness
- Purpura
- Skin ulcers (poor wound healing)
Cushing disease – Laboratory investigation

The diagnosis of Cushing sy. is based on lab documentation of endogenous hypercortisolism:

- Measurements of 24 hours urine free cortisol
- Serum cortisol levels measurements few times a day (midnight!)
- Saliva cortisol concentration
- Dexamethasone supression test
Cushing disease – Laboratory investigation

- Mean basal ACTH levels
- CRH test
- Metopyron test
- Most effective: inferior petrosal venous sampling
  - Before and after CRH administration
Cushing disease – imaging technics

- MRI – sensitivity ~ 50-60%
- ACTH secreting tumors < 5mm
Cushing disease – Treatment

- **Surgical:** Selective transphenoid removal is the treatment of choice!
  - Remission: 80% of micro-, 50% of macroadenoma.
  - After successful surgical tumor resection – postoperative adrenal insufficiency will develop! → cortisol replacement

- **Pituitary irradiation**

- **Medical:** Steroid inhibitors – *ketokonazole* – inhibits P450
  - Metyrapone – inhibits 11β-hydroxylase – normalize plasma cortisol

- **Bilateral adrenalectomy** – predisposes the development of Nelson’s syndrome = rapid pituitary tumor enlargement and ↑ pigmentation (high ACTH)
TSH-secreting adenomas

- <1% of hypophysis adenomas
- Invasive macroadenoma
- TSH $\uparrow$ - T3, T4 $\rightarrow$ Goiter and hyperthyreoidism
- After administration TRH $\rightarrow$ TSH will not elevate
- Tumor also can produce GH or prolactin
- Treatment - surgical
Case history

A 40-year-old woman presents to her doctor with a 12 month history of progressive headaches, weight loss, poor appetite, lethargy, cold intolerance, and amenorrhoea. She has difficulty looking into the periphery when she is driving her car. She has noted a breast discharge and her last menstrual period was 12 months ago. Physical examination is remarkable for bradycardia, weight loss, delayed relaxation of her reflexes, galactorrhoea, and bitemporal haemianopia.
END