ABNORMAL PITUITARY FUNCTION
Specialist Portfolio Seminar
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Overview

• Where/what is the pituitary gland?
• Anterior pituitary overview
• Posterior pituitary overview
• Pituitary dysfunction (example cases)
• Analytical considerations

Located in a bony compartment; cranial fossa beneath hypothalamus
- Connected by pituitary stalk
- Under hypothalamic control

2 lobes:
- Anterior, posterior
- Different functions/hormones secreted

http://www.medguidance.com/thread/Pituitary-Gland.html
Anterior pituitary

- Secretes majority of peptide and glycopeptide (glycoprotein) hormones that control function of peripheral endocrine organs:
  > **Corticotrophs** – Adreno cortical trophic hormone (ACTH)
  > **Lactotrophs** – Prolactin (PRL)
  > **Gonadotrophs** – Luteinizing hormone (LH), Follicle Stimulating Hormone (FSH)
  > **Thyrotrophs** – Thyroid Stimulating Hormone (TSH)
  > **Somatotrophs** – Somatotrophin or Growth Hormone (GH)

- Secretion controlled by releasing and inhibiting factors (predominantly peptides) released into portal circulation from hypothalamus...

- Any disease process that interferes with this blood supply (e.g. non-functioning tumours of pituitary/hypothalamus) will result in severe pituitary function.

### Anterior pituitary systems

#### Anterior pituitary Hormone Functions

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Hormone secreted</th>
<th>Target organ</th>
<th>Effect on target organ</th>
<th>Release stimulated by</th>
<th>Release inhibited by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotroph</td>
<td>ACTH</td>
<td>Adrenal cortex</td>
<td>Production of cortisol</td>
<td>CRH</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Lactotroph</td>
<td>Prolactin</td>
<td>Mammary glands</td>
<td>Milk production/ lactation (in conjunction other hormones)</td>
<td>Suckling</td>
<td>Dopamine</td>
</tr>
<tr>
<td>Gonadotroph</td>
<td>LH &amp; FSH</td>
<td>Gonads (ovaries / testis)</td>
<td>Production of sex steroids (androgens, Estrogens, progesterone)</td>
<td>GnRH</td>
<td>Sex steroids</td>
</tr>
<tr>
<td>Thyrotroph</td>
<td>TSH</td>
<td>Thyroid gland</td>
<td>Production of thyroid hormones T4 &amp; T3</td>
<td>TRH</td>
<td>T4 &amp; T3</td>
</tr>
<tr>
<td>Somatotroph</td>
<td>GH</td>
<td>Liver / Other tissues</td>
<td>Production of IGF-1</td>
<td>GH-RH</td>
<td>Somatostatin</td>
</tr>
</tbody>
</table>
Posterior pituitary

- Embryologically derived from the brain
  - Direct arterial blood supply, not controlled via a portal circulation
- Hormonal secretions directly from nerve terminals of vasopressin (anti-diuretic hormone, ADH) and Oxytocin neurons

**Posterior pituitary Hormone Functions**

<table>
<thead>
<tr>
<th>Hormone secreted</th>
<th>Target organ</th>
<th>Effect on target organ</th>
<th>Release regulated by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytocin</td>
<td>Mammary gland</td>
<td>Milk ejection</td>
<td>Suckling</td>
</tr>
<tr>
<td></td>
<td>Uterus</td>
<td>Uterine contraction</td>
<td>Stretch receptors</td>
</tr>
<tr>
<td>AVP (arginine vasopressin)</td>
<td>Renal collecting duct</td>
<td>Resorption of water (insertion of aquaporin water channels)</td>
<td>Osmoreceptors &amp; baroreceptors</td>
</tr>
<tr>
<td></td>
<td>Smooth muscle</td>
<td>Arteriole &amp; capillary vasoconstriction, also promotes intestinal contraction</td>
<td></td>
</tr>
</tbody>
</table>

- N.B. AVP = ADH (anti-diuretic hormone) = vasopressin

**Examples of Pituitary Dysfunction**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Hormone</th>
<th>Excess or deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior hormones:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactinoma</td>
<td>Prolactin</td>
<td>Excess</td>
</tr>
<tr>
<td>Cushings syndrome (pituitary form)</td>
<td>ACTH</td>
<td>Excess</td>
</tr>
<tr>
<td>Acromegaly / gigantism</td>
<td>GH</td>
<td>Excess</td>
</tr>
<tr>
<td>Hypopopituitarism</td>
<td>One or more pituitary hormones (Pan-hypopopituitarism)</td>
<td>Deficiency</td>
</tr>
<tr>
<td>Growth retardation (uncommon cause)</td>
<td>GH</td>
<td>Deficiency</td>
</tr>
<tr>
<td>Posterior hormones:</td>
<td>AVP</td>
<td>Excess</td>
</tr>
<tr>
<td>SIADH</td>
<td>AVP</td>
<td>Deficiency</td>
</tr>
<tr>
<td>Diabetes Insipidus (cranial form)</td>
<td>AVP</td>
<td>Deficiency</td>
</tr>
</tbody>
</table>
Case 1

- 32 yr male presents to GP
- Clinical details: TATT, on thyroxine, ‘ED’
- Testo very low: 2.0 nmol/L (9.9-27.8)
- LH & FSH added: <1, 2 respectively
- Prolactin added: 9706 mIU/L (73-407)
- Cortisol added: 146 \([11\text{am sample – difficult to interpret}]\)
- Q: Why is the TSH / fT4 not useful in this case?
- Macroprolactin added but prolactin result phoned out anyway – Why?

Hyperprolactinaemia

- Common
- Variable effects:
  - Infertility – in both sexes
  - Amenorrhoea, Galactorrhoea – early indication in women
    - No early signs in men (first signs may be visual disturbance, as below…)
  - Low libido / impotence
- Q: Why might men usually have larger tumours on presentation?
  - If due to a tumour may have direct symptoms from this
    - Headache
    - Visual disturbance
- Q: Why do pituitary tumours cause these symptoms?

Hyperprolactinaemia

- Causes:
  - Dopamine antagonists
  - Other medications (oestrogens)
  - Stress (venepuncture in itself)
  - Pregnancy
  - Elevations in PCOS
  - Renal failure
  - Breast stimulation / chest wall trauma
  - Primary hypothyroidism
  - Pituitary adenoma (commonly microadenoma)
    - Prolactin secreting (see higher prolactin levels)
    - Compression of stalk and inhibition of dopamine action on pituitary

Q: Why do these cause increased prolactin?

“Anti-psychotics” commonly used to treat schizophrenia, bipolar disorder (e.g. clozapine, olanzapine, risperidone).
Anterior pituitary systems

Macroprolactin

- Immunoglobulin (usually IgG) complex with prolactin
- Low bioactivity, i.e. no pathological consequences
- Laboratory artefact
- Should be screened to avoid unnecessary investigations
  - All samples with a total prolactin result >700mIU/L should be tested for macroprolactin

Method:
- Precipitate any high MW complexes with PEG (polyethylene glycol)
- Measure prolactin pre- and post-PEG (accounting for dilution)
- Check recovery of prolactin in the sample
- If macroprolactin present – monomeric prolactin must be reported Q: Why?

Diagnosis of prolactinoma

- Exclude other causes:
  - Pregnancy
  - Medication
  - Stress etc...

- Imaging – MRI pituitary
  - Size defines as macroprolactinoma or microprolactinoma
  - Q: any possibility of confusion with “macroprolactin” here?!

- Pituitary screen
  (check for co-secretion or for loss of function)
  - Baseline pituitary function tests
    - Prolactin
    - TSH & T4
    - Cortisol
    - LH & FSH
    - IGF-1
Treatment
- Medical - Dopamine agonists
  - E.g. Bromocriptine, Cabergoline
  - Especially for microprolactinomas
  - May be used to shrink large prolactinomas before surgery
- Surgical
  - Trans-sphenoidal hypophysectomy = standard procedure
  - NB: Patients given hydrocortisone in case they can’t mount adequate cortisol response to stress of surgery
  - Post-op assessment of pituitary reserve deferred for several days
- Radiotherapy
- Combinations
- Follow up/monitoring
  - E.g. annual DFT of anterior pituitary reserve required after radiotherapy

Case 1 Outcome
- Diagnosed with microprolactinoma
- Treated with cabergoline
- Symptomatically improved
- Prolactin now 149 mIU/L

Case 2
- A previously healthy male patient is diagnosed with persistent hypertension at their GP. They have some baseline bloods done:
  - Na: 143 mmol/L (133-146)
  - K: 3.0 mmol/L (3.5-5.5)
  - Creatinine: 60 µmol/L (44-133)
- On examination the patient shows central obesity with purple stretch marks on their abdomen
- The patient reports weight gain over the past year or so
- The patient mentions that they bruise easily
- In view of the history and results the GP organises some further tests…
  - Q: Any guesses of diagnosis, further tests?
Cushing's Syndrome

- Prolonged exposure of body tissues to excess cortisol
  - 'A Syndrome' – different causes:
    - Pituitary – ACTH secreting tumour = Cushing's disease
    - Adrenal – cortisol secreting tumour
    - Ectopic ACTH production
    - Iatrogenic - Exogenous corticosteroids (most common)
  - Does the patient actually have Cushing's Syndrome?
    - Exclude high BP due to obesity or other causes
    - Check if patient is on steroid medications
    - Then establish cause of cortisol excess…
      - Diagnosis important due to increased CHD risk (CV risk factors)
        therefore prompt treatment required

Differential Diagnosis of Cushing's

1. Confirm excess cortisol:
   - 24 hour urinary free cortisol excretion
     - Excess cortisol rapidly exceeds available capacity of cortisol binding globulin (CBG) – unbound cortisol filtered readily into urine. Multiple collections if possible
   - Midnight salivary cortisol (lose circadian rhythm)
   - Low dose dexamethasone suppression test (DST) – 1mg at 11pm
     - Bloods post dex (~8am) for cortisol measurement – Normal response = Cortisol <50 nmol/L (excludes). Failure to suppress = Diagnostic.
Differential Diagnosis of Cushing’s

2. Measure ACTH:
   • Low/suppressed = appropriate: suggestive of adrenal tumour
   • Normal/Raised = inappropriate: suggestive of excess ACTH
     (Pituitary Cushing’s Disease, ectopic – higher ACTH levels)

3. Further dynamic function testing:
   • High dose DST: suppression of cortisol seen in ~50% pituitary
     adenoma. No response if ectopic ACTH or adrenal tumour

4. Imaging: Pituitary MRI
   • Pituitary lesion present? (i.e. Cushing’s Disease?)

Selective venous sampling with ACTH measurement – to locate
ACTH source (sometimes)

Treatment

• Pituitary tumour:
  › First line = surgery
  › Radiotherapy if not successful

• Medical therapy:
  › Possible for Cushing’s disease of all types but usually for pre-op
    preparation where surgery has failed.
  › Metyroproxone, ketonazole – to maintain circulating [cortisol] between 150-300 nmol/L.
  › If co-secretes prolactin may respond to medical therapy to shrink
tumour first

• Patient’s cured of Cushing’s disease require steroid
replacement therapy and regular monitoring

Case 3

• 45 yr old female patient presents to their GP with headaches.
• She also mentions that her foot size is increasing and her rings no
  longer fit.
• The GP notices that her teeth are slightly spaced on their lower jaw.

Q: Any guesses of diagnosis?
The GP suspects Acromegaly (GH excess)……

- Overgrowth of skeleton & soft tissue coarse facial features; protruding jaw, forehead, hands (‘spade-like’), feet, tongue
- Arthritis, hypertension, sweating, impaired glucose tolerance or DM, CV disease

Gigantism
- If GH excess before long bone growth complete (i.e. childhood)
- Increase in linear growth also observed

http://www.physio-pedia.com/Acromegaly

Causes of Excessive Growth

- Uncommon
- Most often due to GH secreting pituitary tumour (Acromegaly)
- Other causes of tall stature in children (rare):
  - Hyperthyroidism – or hypothyroid children over-treated with thyroxine
  - Inherited Disorders – e.g. Klinefelter’s (47 XXY karyotype)
  - Congenital Adrenal Hyperplasia (CAH)
Diagnosis

- Confirming excess GH
- But... GH secretion episodic & pulsatile
- Therefore single measurement of GH not helpful
  ➔ Use IGF-1 as an indicator of GH status
  ➔ Also used in monitoring of treated acromegaly

- Dynamic function testing: OGTT with GH measurement
  ("Gold standard")
  - Glucose load should suppress GH
  - Acromegaly: GH does not suppress in response to hyperglycaemia
    and may see paradoxical rise in GH

Treatment

- Surgery: First line
  ➔ Trans-sphenoidal hypophysectomy
  ➔ Success depends on size of tumour

- Radiation:
  ➔ Usually reserved for active disease following surgery

- Medical treatment:
  - Dopamine agonists e.g. bromocriptine (if co-secretes prolactin)
  - Somatostatin analogues e.g. octreotide
  - GH-receptor antagonist: pegvisomant

Anterior pituitary systems
Case 4
- A 50 yr old male patient was diagnosed with a prolactinoma
- Following treatment with cabergoline to shrink the tumour he underwent pituitary surgery
- What is he now at risk of?

Hypopituitarism
- Deficiencies in one or more of the pituitary hormones

Causes:
- Pituitary or non-pituitary tumours
- Infiltrative processes e.g. sarcoidosis, haemochromatosis
- Infections e.g. cerebral abscess, meningitis, syphilis.
- Ischaemia and infarction e.g. Sheehan's syndrome (postpartum haemorrhage), pituitary apoplexy (caused by an acute infarction of a pituitary adenoma)
- Iatrogenic e.g. irradiation, neurosurgery
- Head injury (may have occurred up to several years before)
- Autoimmune

Case: post pituitary surgery
- Check remaining pituitary function
- May be transient or permanent loss of function in one or more axis
- Q: What is the most important pituitary hormone system to check?
- ACTH: check by measuring 9am cortisol and SST if necessary
- If cortisol is low: steroid cover to avoid adrenal crisis
- Recheck for recovery later
- Remaining axis should be tested ~1 month post surgery
- N.B. Post-irradiation pituitary function should be assessed regularly (~6 monthly)
Diagnosis of Hypopituitarism

- Dependent upon patient history for degree of investigation

Example first line screen:

- 9 am cortisol
- TSH & fT4
- Pituitary-gonadal axis:
  - Females – regular menstrual cycle indicates intact axis
  - Otherwise check LH/FSH & oestradiol in females
  - Check LH/FSH & testosterone in males
- Prolactin

- Serum Na – although patients with 2ndry adrenal insufficiency don’t usually develop severe electrolyte disturbances.

Depending on baseline results:
- DFTs e.g. SST, GnRH test, TRH test

Case 5

- Patient in hospital with pneumonia
- Persistent hyponatraemia

- Results:
  - Serum Na 126 mmol/L (133-146)
  - Serum osmolality 258 mOsm/kg (275-295)
  - Urine osmolality 300 mOsm/kg (50-1500)
  - Urine Na 60 mmol/L

- Are the urine results appropriate? Why not?

SIADH criteria

- Most common cause of hyponatraemia in hospitalised patients BUT other causes must be ruled out

Criteria for diagnosis: (Diagnosis of exclusion)

- Clinically euolaemic patient
- Patient not on diuretics
- Hyponatraemia with low serum osmolality
- Normal renal, adrenal, cardiac, hepatic and pituitary function
- Urine osmolality less than maximally dilute
- Inappropriately high urine sodium (e.g. >20-40 mmol/L)
- Respond to water restriction (inc. plasma osmo and [Na])
SIADH

- Inappropriate AVP/ADH i.e. retention of water despite low serum osmolality & normal/increased plasma volume

Common causes

- Many drugs including tricyclic antidepressants, carbamazepine, omeprazole, vincristine, ACE inhibitors, narcotics, nicotine
- Post-operative stress
- CNS disturbances e.g. infections, stroke, trauma
- Pulmonary disorders e.g. smoking, pneumonia, tuberculosis, emphysema

Treatment of SIADH

- Fluid restriction (to increase plasma osmo/[Na])
- Underlying cause
- V2 receptor antagonist

Case 6

- A patient presents to their GP complaining of excessive urination (polyuria) and thirst (polydipsia)
- On questioning, the onset followed a car accident where they suffered a head injury.
- The GP organises some tests:
  - Serum ??
  - Urine ??
  - Serum U&E's are normal
- 24 hour urine collection comprises 6 L
# Diabetes Insipidus

- **Definition:** Excretion of excess, dilute urine in excess of 3L/24 hours or >40ml/L/Kg/24h (>100ml/Kg/24h in infants)
- **Two types:**
  - Central or Cranial DI (deficient AVP production)
  - Nephrogenic DI (resistance to AVP)
- **Can be inherited or acquired**
- **Differential diagnosis:**
  - Psychogenic polydipsia
  - Osmotic diuresis

## Causes of DI

- **Central/Cranial (Hypothalamic) – Impairment of osmoregulated AVP production**
  - **Secondary causes** – Trauma (head injury, surgery), Tumours (germ cell, metastatic, pituitary adenoma), Inflammation (meningitis, encephalitis, sarcoid, Guillain-Barré), Vascular (aneurysm, Infarction), Pregnancy
- **Nephrogenic – Resistance to anti-diuretic effects of AVP**
  - **Primary Causes** – Genetic: X-linked recessive V2-R defect, aut dom/aut rec AQP2 defect, Idiopathic
  - **Secondary causes** – Chronic renal disease, drugs (e.g. lithium, demeclocycline), Systemic (sarcoidosis, myelomatosis), Pregnancy
- **Dipsogenic (primary polydipsia) – primary excessive inappropriate drinking, normal AVP secretion/action**
  - Compulsive water drinking associated with affective disorders e.g. drugs, structural/organic hypothalamic disease (tumour sarcoidosis, tuberculous meningitis, head injury)

## Diagnosis DI

- **Confirm high urine output (distinguish frequency vs volume)**
- **Baseline tests:**
  - Serum U&E
  - Serum osmolality – clue = initial low osmolality if dipsogenic
  - Early morning urine osmolality
    - N.B. early morning may help distinguish if excess water intake
- **Exclude other causes:**
  - HbA1c / fasting glucose = diabetes
  - 9am cortisol = adrenal insufficiency
  - TSH = thyroid dysfunction
- **Water deprivation test to distinguish between types...**
Water deprivation test

Preparation
- Give hormone injections commencing the night before
- Fast the patient and calculate 90% of total body weight
- Administration of GHD, dopaminergic, or AVP ganoitin
- Blood and urine should be obtained
- Start at 0800 on the day of the test
- Hair should be removed from the site needle

Procedure
- One patient weight, two patients, and a constant urine test
- At 4 hours: first urine from 0800
- At 8 hours: second urine from 1200

Premao in 24-hour test (in case of acute: can be -30% monthly, over 2 consecutive urina samples or case above anomaly test is defined as a 25% increase in 24-hour fluid intake)

SWBH protocol

Water deprivation test

Interpretation of water deprivation test

<table>
<thead>
<tr>
<th>Fasting Desmopressin</th>
<th>Post DESOMOPRESSIN</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Osmolality</td>
<td>Urine Osmolality</td>
<td>Urine Osmolality</td>
</tr>
<tr>
<td>&lt;200 250</td>
<td>&gt;150</td>
<td>&lt;350</td>
</tr>
<tr>
<td>&gt;250</td>
<td>&lt;300</td>
<td>&lt;350</td>
</tr>
<tr>
<td>&gt;250 300-700</td>
<td>&gt;350</td>
<td>&gt;350</td>
</tr>
<tr>
<td>&gt;250 300-700</td>
<td>&gt;350</td>
<td>Partial nephrogenic DI or primary polydypsia</td>
</tr>
</tbody>
</table>

Further Investigations…

- Cranial/Central: MRI head, anterior pituitary function, AVP abs
- Nephrogenic: Renal U/S, exclude tubulopathies, urine microscopy, genetic studies
- Dipsogenic: MRI head
Treatment

• Cranial DI:
  • Avoid severe dehydration
  • Primary cause
  • Replace the hormone – DDAVP (desmospray/desmopressin)
  • Medicalert bracelet/pendant

• N.B. Nephrogenic DI cannot do this
  • Primary cause
  • Manage water intake
  • Medicalert bracelet/pendant

• Dipsogenic: Primary cause, restrict fluid intake

Pre-analytical considerations

• ACTH
  • Rapidly degraded
  • Sensitive to freeze-thaw cycles

• AVP
  • Rapidly degraded
  • Limited assays available, no standardisation

• Circadian rhythms
  • Cortisol as a measure of ACTH function

• Pulsatile secretion
  • GnRH & LH, GH

Analytical considerations:

All are peptide hormones:
• Prolactin
• GH
• ACTH
• AVP
• Oxytocin

Some are glycoproteins:
• FSH
• LH
• TSH
  share alpha subunit, also hCG
Assays

- 2-site immunoassays

Interferences:
- Hook effect
- Macroprolactin

Standardisation

Why does this matter?
- Standardisation challenging for peptide hormones
- Definition of standard material – different circulating forms
- Immunoassays: different manufacturers use different antibodies against different epitopes
- Different buffers etc

Standardisation

E.g. GH

- Different forms
  - ~75% circulate in original 22kDa form
  - Also post-translation modification: 20kDa form
  - Also dimers and complexed with binding protein

- Assays now standardised to 22kDa form but may still show different cross-reactivity

- Method-specific cut-offs should be used for interpretation

- Also differing glycosylation of circulating glycoproteins to recombinant standards e.g. LH, FSH

Rarely measured

AVP
- Stability
  - Sample must be separated & stored frozen until analysis
  - Limited assay availability, RIA
- Long TAT
- Useful?
- Standardisation?!

Oxytocin
- No relevance to reproductive disorders
References/Further Reading

- Text books:
  - Clinical Biochemistry (Allan Gaw et al, third edition)
  - Clinical Biochemistry: Metabolic and Clinical Aspects (Marshall and Bangert)
  - Tietz (Methodology)

- Abbott Kit inserts (peptide hormones)