ABNORMAL PITUITARY FUNCTION

Specialist Portfolio Seminar

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Overview

- Anterior pituitary overview
- Posterior pituitary overview
- Pituitary dysfunction (example cases)
- Analytical considerations
- Questions

Anterior pituitary systems

Anterior pituitary

<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 gland</td>
<td>Production of cortisol</td>
<td>CRH</td>
<td>Corticotropin</td>
</tr>
<tr>
<td>Lactotroph</td>
<td>Prolactin</td>
<td>Mammary glands</td>
<td>Milk production (in conjunction with other hormones)</td>
<td>TRH</td>
<td>Dopamine</td>
</tr>
<tr>
<td>Gonadotroph</td>
<td>LH &amp; FSH</td>
<td>Gonads (ovaries / testes)</td>
<td>Production of sex steroids</td>
<td>LH &amp; TRH</td>
<td></td>
</tr>
<tr>
<td>Thyrotroph</td>
<td>TSH</td>
<td>Thyroid gland</td>
<td>Production of thyroid hormones</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 directly stimulates growth</td>
<td>GHRH</td>
<td>Somatostatin</td>
</tr>
</tbody>
</table>

Posterior pituitary

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

Posterior pituitary

<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>AVP (arginine vasopressin)</td>
<td>Uterus</td>
<td>Contraction</td>
<td>Smooth receptors</td>
</tr>
<tr>
<td></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>Aorta &amp; capillary vasoconstriction, also promotes intestinal contraction</td>
<td></td>
</tr>
</tbody>
</table>

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

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>Cushing’s 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>Hypopituitarism</td>
<td>One or more pituitary hormones</td>
<td>Deficiency</td>
</tr>
<tr>
<td>Growth retardation (uncommon cause)</td>
<td>GH</td>
<td>Deficiency</td>
</tr>
</tbody>
</table>

| Posterior hormones: | | |
| SIADH | AVP | Excess |
| DI (cranial form) | AVP | Deficiency |

Case 1

- 32 yr male presents to GP
- Clinical details: TAT, on thyroxine
- 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 [11am 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

- Variable effects:
  - Amenorrhoea
  - Infertility
  - Galactorrhoea
  - 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 | Why do these cause increased prolactin? |
| Other medications | |
| Stress | |
| Pregnancy | |
| Elevations in PCOS | |
| Renal failure | |
| Breast stimulation / chest wall trauma | |
| Primary hypothyroidism | Why does this cause increased prolactin? |
| Pituitary adenoma | |
| Prolactin secreting | |
| Compression of stalk and inhibition of dopamine action on pituitary | |
Anterior pituitary systems

Macroprolactin
- IgG complex with prolactin
- Low bioactivity, i.e. no pathological consequences
- Laboratory artefact
- Should be screened to avoid unnecessary investigations

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

Diagnosis of prolactinoma
- Exclude other causes:
  - Pregnancy
  - Medication
- Imaging – MRI pituitary
  - Size defines as macroprolactinoma or microprolactinoma
- Pituitary screen
  (check for co-secretion or for loss of function)
  - Prolactin
  - TSH & FT4
  - Cortisol
  - LH & FSH
  - IGF-1
  Q: any possibility of confusion with “macroprolactin” here?!

Treatment
- Medical
  - dopamine agonists
  Q: Why does this work?
- Surgical
- Radiotherapy
- Combinations
- Follow up

Case conclusion
- Diagnosed with microprolactinoma
- Treated with cabergoline
- Symptomatically improved
- Prolactin now 149 mU/L

Case 2
- A previously healthy male patient is diagnosed with hypertension at their GP. They have some baseline bloods:
  - Na: 143 mmol/L (133-146)
  - K: 3.0 mmol/L (3.5-5.3)
  - 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…
Cushing’s syndrome

- Syndrome i.e. different causes:
  - Pituitary – ACTH secreting tumour = Cushing’s disease
  - Adrenal – cortisol secreting tumour
  - Ectopic ACTH production
  - Exogenous corticosteroids

Diagnosis

1. Confirm excess cortisol:
   - 24 hour urinary cortisol excretion
   - Midnight salivary cortisol (lose circadian rhythm)
   - Low dose dexamethasone suppression test (DST)

2. Measure ACTH:
   - Low = appropriate: suggestive of adrenal tumour
   - Normal - High = inappropriate: suggestive of excess ACTH (pituitary or ectopic)

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

4. Imaging: Pituitary MRI
   - Pituitary lesion present?

Case 3

- 45 yr old female patient presents to their GP due to headaches
- They also mention that their foot size is increasing and their rings no longer fit
- The GP notices that their teeth are slightly spaced on their lower jaw
- The GP suspects acromegaly (GH excess)

Acromegaly

- Overgrowth of skeleton & soft tissue
- Jaw, forehead, hands, feet, tongue

Gigantism

- If GH excess before long bone growth complete
- Increase in linear growth also observed
Why headaches & visual defects?

Important to recognise and treat

Diagnosis

- Excess GH
- But… GH secretion episodic & pulsatile
- Therefore single measurement of GH not helpful
  - Use IGF-1 as an indicator of GH status
- Dynamic function testing: OGTT.
  - Glucose load should suppress GH
  - Acromegaly: GH does not suppress

Treatment

- Surgery
- Medical treatment:
  - Dopamine agonists (if co-secretes prolactin)
  - Somatostatin analogues
  - 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
  - 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
  - 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
  - Progesterone
  - Serum Na

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:
- Clinically euvoalaemic patient
- Patient not on diuretics
- Hyponatraemia with low serum osmolality
- Normal renal, adrenal and thyroid function
- Urine osmolality less than maximally dilute
- Inappropriately high urine sodium (e.g. >40 mmol/L)

SIADH

- Inappropriate AVP 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. pneumonia, tuberculosis, emphysema

Treatment

- Fluid restriction
- Underlying cause
- V2 receptor antagonist
Case 6

- A patient presents to their GP complaining of excessive urination.
- 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

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

Diagnosis DI

- Confirm high urine output (distinguish frequency / volume)
- Baseline tests:
  - Serum U&E
  - Serum osmolality
  - 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

- Cranial DI: replace the hormone
  - DDAVP
- N.B. Nephrogenic DI cannot do this
  - Manage water 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

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

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

Knowledge assessment to follow…