Non-Functioning Tumours and Pituitary Hormone Testing

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Agenda

• Pituitary masses
• Non functioning pituitary adenomas
• Testing pituitary function
• Pituitary Hormone Replacement
Anatomy

• Anterior lobe: glandular tissue, accounts for 75% of total weight.

• Posterior: nerve tissue & contains axons that originate in the hypothalamus.
MRI of normal pituitary gland – Parasellar area

- Anterior pituitary
- Posterior Pituitary
- Optic chiasm
- Hypothalamus
- Pituitary stalk
Pituitary Mass Lesion

• Non-Functioning Pituitary Adenomas

• Endocrine active pituitary adenomas

• Malignant pituitary tumors: Functional and non-functional pituitary carcinoma

• Metastases in the pituitary (breast, lung, stomach, kidney)

• Pituitary cysts: Rathke's cleft cyst, Mucocoeles, Others
Pituitary Mass Lesion

• Developmental abnormalities: Craniopharyngioma (occasionally intrasellar location), Germinoma, Others

• Primary Tumors of the central nervous system: Perisellar meningioma, Optic glioma, Others

• Vascular tumors: Hemangioblastoma, Others

• Malignant systemic diseases: Hodgkin's disease, Non-Hodgkin lymphoma, Leukemic infiltration, Histiocytosis X

• Granulomatous diseases: Neurosarcoidosis, Wegner's granulomatosis, Tuberculosis, Syphilis

• Vascular aneurysms (intrasellar location)
Pituitary Mass Lesion

- Pituitary Adenoma
- Craniopharyngioma
- Pituitary Adenoma
- Lymphocytic Hypophysitis
Development of the Pituitary Gland

- **Infundibulum**
- **Rathke's pocket**
- **Stalk of Rathke's pouch** (degenerating)
- **Intermediate lobe**
- **Anterior lobe**
- **Hypothalamus**
- **Infundibulum**
- **Neural lobe**
- **Residual lumen**
- **Stalk of Rathke's pouch** (former site of)
Craniopharyngioma

- Arise from squamous epithelial remnants of Rathke’s pouch
  - Adamantinous: cyst formation and calcification
  - Squamous papillary: well circumscribed

- Benign tumour although infiltrates surrounding structures

- Peak ages: 5 to 14 years; 50 to 74 years

- Solid, cystic, mixed, extends into suprasellar region

- Raised ICP, visual disturbances, growth failure, pituitary hormone deficiency, weight increase
Sagittal enhanced T1-weighted image of a solidly enhancing craniopharyngioma
Sagittal unenhanced T1-weighted image of a craniopharyngioma.

Cystic mass
Rathke’s Cyst

• Derived from remnants of Rathke’s pouch

• Single layer of epithelial cells with mucoid, cellular, or serous components in cyst fluid

• Mostly intrasellar component, may extend into parasellar area

• Mostly asymptomatic and small

• Present with headache and amenorrhoea, hypopituitarism and hydrocephalus
Meningioma

• Commonest tumour of region after pituitary adenoma
• Complication of radiotherapy
• Associated with visual disturbance and endocrine dysfunction
• Usually present with loss of visual acuity, endocrine dysfunction and visual field defects
• T1 MRI images similar to grey matter, hypointense to pituitary and enhance with contrast
Meningioma
Lymphocytic Hypophysitis

- Inflammation of the pituitary gland due to an autoimmune reaction
  - Lymphocytic adenohypophysitis
  - Lymphocytic infundibuloneurohypophysitis
  - Lymphocytic panhypophysitis

- Incidence 1 per 9 million based on pituitary surgery

- LAH commoner in women - 6:1

- Age of presentation of LAH women: 35 years; men: 45 years
  - Pregnancy or postpartum
Lymphocytic Hypophysitis

- Hypointense on T1 imaging
- Hyperintense on T2 imaging
- Stalk enlargement
- Pituitary enlargement
Non-Functioning Pituitary Adenoma (NFPA)

- Pituitary adenomas account for <10 – 15% of primary intracranial tumours
- NFPA account for 14 - 28% of clinically relevant pituitary adenomas and 50% of pituitary macroadenomas
- Most NFPA express gonadotropins or subunits
- 30% of NFPA are classified as null cell adenomas
Non-Functioning Pituitary Adenoma

• Diagnosed between 20 and 60 years of age in 78% of cases
• 50% of NFPA are incidentalomas
• 50% of macroadenomas have visual disturbances and 50% have headaches
• Signs of aggressiveness
  – Large size
  – Cavernous sinus invasion
  – Lobulated suprasellar margins
Pituitary Dysfunction

- Tumour mass effects
- Hormone excess
- Hormone Deficiency

Investigations
- Hormonal tests
- If hormonal tests abnormal or tumour mass effects perform MRI pituitary
Local Mass effects

Cranial Nerve Palsy and Temporal Lobe Epilepsy

Visual Field Defects

Headaches

CSF rhinorrhoea
Measuring Visual Field defects
Measuring Visual Field defects

Visual pathway

Visual field defects

Example of lesion

1. Normal
   - Left optic nerve compression
   - Chiasmal compression from pituitary tumour

2. Unilateral field loss
   - Bitemporal hemianopia

3. Homonymous hemianopia
   - Left cerebrovascular event
Hormonal Secretion

- Stimuli
- Anterior pituitary
- Hormones:
  - Gonadotropins
  - FSH and LH
  - Growth hormone
  - GH
  - Prolactin
- Hormones:
  - Thyroid-stimulating hormone (TSH)
  - Melanocyte-stimulating hormone (MSH)
  - Adrenocorticotropic hormone (ACTH)
  - Prolactin (PRL)
Non-Functioning Tumours

- No specific test but absence of hormone secretion
- Test normal pituitary function
- Trans-sphenoidal surgery if threatening eyesight or progressively increasing in size
Testing Pituitary Function

• Complex because:
  – Many hormones: GH, LH/FSH, ACTH, TSH and ADH
  – May have deficiency of one or all and may be borderline
  – Circadian rhythms and pulsatile

• Guiding principle:
  – If the peripheral target organ is working normally the pituitary is working
Testing Pituitary-Thyroid Axis

- Primary Hypothyroid - Raised TSH low Ft4
- Hypopituitary - Low Ft4 with normal or low TSH
- Graves disease (toxic) - Suppressed TSH high Ft4
- TSHoma (very rare) - High Ft4 with normal or high TSH
- Hormone resistance - High Ft4 with normal or high TSH

- Measure Ft4 in pituitary disease
Testing Gonadal Axis: Men

- **Primary Hypogonadism** - Low T raised LH/FSH
- **Hypopituitary** - Low T normal or low LH/FSH
- **Anabolic use** - Low T and suppressed LH
- **Measure 0900h fasted T and LH/FSH in pituitary disease**
Testing Gonadal Women: Female

- **Before puberty** - Oestradiol very low/undetectable with low LH and FSH although FSH slightly higher than LH

- **Puberty** - Pulsatile LH increases and oestradiol increases

- **Post menarche** - Monthly menstrual cycle with LH/FSH, mid-cycle surge in LH and FSH and levels of oestradiol increase through cycle

- **Primary ovarian failure** (includes menopause) - High LH and FSH with FSH greater than LH and low oestradiol

- **Hypopituitary** - Oligo or amenorrhoea with low oestradiol and normal or low LH and FSH
Testing the HPA axis

- Circadian Rhythm
- Measure 0900h cortisol and synacthen
- **Primary AI:** Low cortisol, high ACTH, poor response to Synacthen
- **Hypopituitarism:** Low cortisol, low or normal ACTH, poor response to synacthen
Testing GH/IGF1 axis

- GH is secreted in pulses with greatest pulse at night and low or undetectable levels between pulses
- GH levels fall with age and are low in obesity
- **Measure: IGF-I and GH stimulation test**
  - Insulin stress test
  - Glucagon test
  - Other
Prolactin levels

- Prolactin under negative control of dopamine
- Prolactin is a stress hormone
- Measure prolactin or cannulated prolactin (3 samples over an hour to exclude stress of venepuncture)
- Prolactin may be raised because of:
  - Stress
  - Drugs: antipsychotics
  - Stalk pressure
  - Prolactinoma
Investigation of DI - water deprivation test

NDI = nephrogenic DI
CDI = cranial DI
Dynamic Testing

Dynamic stimulation/suppression testing may be useful in select cases to further evaluate pituitary reserve and/or for pituitary hyperfunction

- Dexamethasone suppression testing – Cushing’s
- Oral glucose GH suppression test - Acromegaly
- CRH stimulation – Cushing’s
- TRH stimulation – TSHoma
- GnRH stimulation – gonadotrophin deficiency
- Insulin-induced hypoglycemia – GH/ACTH deficiency
- Glucagon test – GH deficiency
Radiologic Evaluation: MRI

- Preferred imaging study for the pituitary
- Better visualization of soft tissues and vascular structures than CT
- No exposure to ionizing radiation
- T1-weighted images produce high–signal intensity images of fat. Structures such as fatty marrow and orbital fat show up as bright images.
- T2-weighted images produce high-intensity signals of structures with high water content, such as cerebrospinal fluid and cystic lesions
Radiologic Evaluation: CT

- Better at visualizing bony structures and calcifications within soft tissues

- Better at determining diagnosis of tumors with calcification, such as germinomas, craniopharyngiomas, and meningiomas

- May be useful when MRI is contraindicated, such as in patients with pacemakers or metallic implants in the brain or eyes

- Disadvantages include:
  - less optimal soft tissue imaging compared to MRI
  - use of intravenous contrast media
  - exposure to radiation
Craniopharyngioma on CT
Pituitary Hormone Deficiency

**GH**
- Short stature
- Abnormal body composition
- Reduced Muscle Mass
- Poor Quality of Life
- Rx: Growth Hormone

**LH/FSH**
- Hypogonadism
- Reduced Sperm Count
- Infertility
- Menstruation Problems
- Rx: Testosterone in males; oestradiol ± progesterone in females

**TSH**
- Hypothyroidism
- Rx: Levothyroxine

**ACTH**
- Adrenal Failure
- Decreased Pigment
- Rx: Hydrocortisone

**ADH**
- Diabetes Insipidus (ADH deficiency - Decreased water absorption in kidney resulting in polyuria & polydipsia)
- Rx: DDAVP
Current Hydrocortisone Replacement Therapy
Inadequate & non-circadian

Absence of early morning (before wake-up) exposure to cortisol
Microparticulate: Modified-Release HC

Challenge: gut length and transit time

Solution: microparticulates
Twice daily microparticulate formulation

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<th>Geomean / Median 10 &amp; 90&lt;sup&gt;th&lt;/sup&gt; Centile</th>
<th>Cmax nmol/l</th>
<th>Tmax (hr)</th>
<th>AUCo-24h hr*nmol/l</th>
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<td>DIURF-006, 20+10mg (n=16)</td>
<td>665 (477-871)</td>
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<td>Normative data (n=28)</td>
<td>594 (409-973)</td>
<td>0812 (0536 - 0936h)</td>
<td>4706 (3242-6588)</td>
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Whitaker et al., Clin Endo 2013
Thyroxine replacement

• Dose 1.6 micrograms/kg/day

• Aim to achieve levels to mid to upper half of reference range

• Check level before levothyroxine dose

• Higher doses usually required in patients on oestrogens or in pregnancy
Growth hormone replacement

• < 60 years – start 0.2 – 0.4mg/day
• > 60 years – start 0.1 – 0.2 mg/day

• Aiming for mid-range IGF1 levels

• Measure IGF1 6 weeks after dose start and change

• Improves lipid profiles, body composition and bone mineral density
Testosterone replacement

• Different types of formulations: gels, injections, oral

• Follow Testosterone levels, Full Blood Count and Prostate Specific Antigen

• Improve bone mineral density, libido, function, energy levels and sense of well being, muscle mass and reduce fat
Oestrogen Replacement

- Oral oestrogen or combined oestrogen/progestogen formulations (also transdermal, topical gels, intravaginal creams)

- Alleviate flushes and night sweats; improve vaginal atrophy

- Reduce risk of cardiovascular disease, osteoporosis and mortality

- HRT in 40 to 49 year olds is not associated with breast cancer
Desmopressin

- Different formulations: subcutaneously, orally, intra-nasally, sub-lingually

- Adjust according to symptoms

- Monitor sodium levels
Conclusion

• Pituitary lesions may present with compressive symptoms, excess hormone production

• Establishing diagnosis biochemically is crucial prior to radiological investigations

• Pituitary hormone replacement mosy importantly helps improve quality of life and gives an important sense of well being