HYPOTHALAMUS AND THE PITUITARY GLAND

-The pituitary plays a central role in several major endocrine axes, so that investigation and treatment invariably involves several other glands

-The pituitary gland is enclosed in the sella turcica and bridged over by a fold of dura mater called the diaphragma sellae, with the sphenoidal air sinuses below and the optic chiasm above. The cavernous sinuses are lateral to the pituitary fossa and contain the 3rd, 4th and 6th cranial nerves and the internal carotid arteries.

-The gland is composed of two lobes, anterior and posterior, and is connected to the hypothalamus by the infundibular stalk, which has portal vessels carrying blood from the median eminence of the hypothalamus to the anterior lobe and nerve fibres to the posterior lobe

Anterior pituitary gland

--prolactin is not secreted in pulsatile fashion,

--growth hormone is secreted in a pulsatile fashion.

--Similarly, in suspected ACTH-dependent Cushing's disease ,random measurement of plasma cortisol is unreliable and the diagnosis is usually made .by a dexamethasone suppression test

.-- Local complications of a large pituitary tumour most commonly reflect compression of the optic pathway. A pituitary tumour may be classified as either a macroadenoma (> 10 mm diameter) or a microadenoma (< 10 mm diameter).

-- Microadenomas are not associated with hypopituitarism or compression of .local structures and are only treated if they are secreting excess hormones.

--Surgical biopsy is usually only performed as part of a therapeutic operation.

--Conventional staining identifies pituitary tumours as either chromophobe, acidophil or basophil.

Posterior pituitary and hypothalamus

-Patients with hypothalamic disease are at risk of anterior pituitary dysfunction

-In addition, these patients may have posterior pituitary dysfunction.

-the posterior pituitary is rarely affected by pituitary tumours, and dysfunction most commonly occurs following pituitary surgery.

-In practice, the only posterior pituitary function requiring investigation is deficiency of vasopressin resulting in diabetes insipidus

ANTERIOR PITUITARY HORMONE DEFICIENCY

The term 'hypopituitarism' means the combined deficiency of any of the anterior pituitary hormones. This most commonly results from the destructive effects of a pituitary macroadenoma

. CAUSES OF ANTERIOR PITUITARY HORMONE DEFICIENCY

---Structural

Primary pituitary tumour-

Adenoma, Carcinoma exceptionally rare

--Secondary tumour (including leukaemia and lymphoma, Craniopharyngioma Meningioma, Haemorrhage (apoplexy

---Inflammatory/infiltrative Sarcoidosis,Lymphocytic hypophysitis Haemochromatosis

-Infections, e.g. pituitary abscess, TB, syphilis, encephalitis

---Congenital deficiencies

GnRH (Kallmann's syndrome)*-gonadotrophin-releasing hormone

GHRH*-growth hormone-releasing hormone

TRH-thyrotrophin-releasing hormone

CRH-corticotrophin-releasing hormone

---Functional* Chronic systemic illness

Anorexia nervosa

Excessive exercise

---Other

*Head injury

*Para-sellar surgery)

*Parasellar radiotherapy)

Post-partum necrosis (Sheehan's syndrome

Clinical assessment

- The presentation is highly variable and depends on the underlying lesion and the pattern of resulting hormone deficiency.
- -With progressive lesions of the pituitary there is a characteristic sequence of loss of pituitary hormone secretion. Growth hormone secretion is often the earliest to be lost. In adults, this produces lethargy, muscle weakness and increased fat mass, but these features are not obvious in isolation Next, -.gonadotrophin (LH and FSH) secretion becomes impaired
- -The next hormone to be lost is usually ACTH, resulting in symptoms of cortisol insufficiency.
- --In contrast to the pigmentation of Addison's disease, a striking degree of pallor is usually present, principally because of lack of stimulation of melanocytes by β-lipotrophic hormone (β-LPH, a fragment of the ACTH precursor peptide) in the skin

.

Finally, TSH secretion is lost with consequent secondary hypothyroidism.

-This contributes further to apathy and cold intolerance.

-In contrast to primary hypothyroidism, frank myxoedema is rare, because the thyroid retains some autonomous function

-The onset of all of the above symptoms is insidious. However, patients sometimes present acutely unwell with adrenocortical insufficiency. This may be precipitated by a mild infection or injury, or may occur secondary to pituitary apoplexy

Investigations

-In acutely unwell patients, the priority is to diagnose and treat cortisol deficiency. Other tests can be undertaken later.

-More specialised biochemical tests, such as insulin tolerance tests, GnRH and TRH tests, are rarely required.

-All patients with biochemical evidence of pituitary hormone deficiency should have an MRI or CT scan to identify pituitary or hypothalamic tumours.

- If a tumour is not identified, then further investigations are indicated to exclude infectious or infiltrative causes

INSULIN TOLERANCE TEST

Use

Assessment of the hypothalamic-pituitary-adrenal axis

Assessment of growth hormone deficiency

Contraindications

-Ischaemic heart disease

-Epilepsy

-Severe hypopituitarism (0800 hrs plasma cortisol < 180 nmol/l or 6.6 μg/dl

Dose

. 0.15 U/kg body weight soluble insulin i.v

To produce adequate hypoglycaemia (tachycardia and sweating-with blood glucose < 2.2 mmol/l (40 mg/dl

Blood samples 0, 30, 45, 60, 90, 120 minutes for blood glucose, plasma cortisol and growth hormone

Results

Normal subjects GH > 20 mU/l (6.7 ng/ml-

Normal subjects cortisol > 550 nmol/l (~20.2 μg/dl

TESTS OF GROWTH HORMONE SECRETION

- GH levels are commonly undetectable, so a choice from the range of 'stimulation' tests is required:
  - --1hour after going to sleep
  - --Frequent sampling during sleep
  - --Post-exercise
  - --Insulin-induced hypoglycaemia

Management

-Treatment of acutely ill patients is similar to adrenocortical insufficiency,

-Chronic hormone replacement therapies are required

---Cortisol replacement

.---Mineralocorticoid replacement is not required

---Thyroid hormone replacement

Unlike in primary hypothyroidism, measuring TSH is not helpful in adjusting the replacement dose,

It is dangerous to give thyroid replacement to patients with adrenal insufficiency without first giving glucocorticoid therapy, since this may .precipitate adrenal crisis

---Sex hormone replacement

This is indicated if there is gonadotrophin deficiency in men of any age and in women under the age of 50 to restore normal sexual function and to prevent osteoporosis

DIABETES INSIPIDUS

- This uncommon disorder is characterised by the persistent excretion of excessive quantities of dilute urine, and by thirst.
- -It can be classified as cranial diabetes insipidus, in which there is deficient production of ADH by the hypothalamus, and nephrogenic diabetes insipidus, in which the renal tubules are unresponsive to ADH

Causes of diabetes insipidus are

---Cranial

-Structural hypothalamic or high stalk lesion

-Idiopathic

-Genetic defect

Dominant •

Recessive (DIDMOAD syndrome-association of diabetes insipidus with diabetes mellitus, optic atrophy, deafness

--

Nephrogenic

--Genetic defect

--Metabolic abnormality

Hypokalaemia

Hypercalcaemia

--Drug therapy

Lithium

Demeclocycline

--Poisoning

Heavy metals

--Chronic kidney disease

Polycystic kidney disease

Sickle-cell anaemia

Infiltrative disease

Clinical assessment

-The most marked symptoms are polyuria and polydipsia. The patient may pass 5-20 litres or more of urine in 24 hours. This is of low specific gravity and osmolality.

-If the patient has an intact thirst mechanism, is conscious and has access to oral fluids, then he or she can maintain adequate fluid intake.

-The differential diagnosis of diabetes insipidus includes diabetes mellitus and primary polydipsia, a condition that is seen most often in patients with established psychiatric disease.

Investigations

WATER DEPRIVATION TEST

To establish a diagnosis of diabetes insipidus, and differentiate cranial from nephrogenic causes

protocol

--No coffee, tea or smoking on the test day

--Free fluids until 0730 hrs on the morning of the test

--No fluids from 0730 hrs

-- at 0830 hrs for body weight, plasma and urine osmolality

--Record body weight, urine volume, urine and plasma osmolality every 2 hours for up to 8 hours

--Stop the test if the patient loses 3% of body weight

If plasma osmolality reaches > 300 mOsm/kg and urine osmolality < 600 .--mOsm/kg, then administer DDAVP 2 μg i.m

Interpretation

-- Diabetes insipidus is confirmed by a plasma osmolality > 300 mOsm/kg with a urine osmolality < 600 mOsm/kg

--Cranial diabetes insipidus is confirmed if urine osmolality rises by at least 50% after DDAVP

--Nephrogenic diabetes insipidus is confirmed if DDAVP does not concentrate the urine

--Primary polydipsia is suggested by low plasma -- osmolality at the start of the test

Management

-Treatment of cranial diabetes insipidus is with des-amino-des-aspartate-arginine vasopressin (desmopressin, DDAVP), an analogue of ADH with a longer half-life. ------

-Polyuria in nephrogenic diabetes insipidus is improved by thiazide diuretics (e.g. bendroflumethiazide 2.5-5 mg/day), amiloride (5-10 mg/day) and NSAIDs (e.g. indomethacin 15 mg 8-hourly), although the last of these carries a risk of reducing glomerular filtration rate.

HYPERPROLACTINAEMIA

-Hyperprolactinaemia is a common biochemical abnormality.

-The cardinal features are galactorrhoea and hypogonadism.

-Prolactin stimulates milk secretion but not breast development, so that galactorrhoea almost never occurs in men, and is only possible in those in whom gynaecomastia is induced by hypogonadism

CAUSES OF HYPERPROLACTINAEMIA

-Physiological

Stress (e.g. post-seizure, Pregnancy, Lactation,Nipple stimulation ,Sleep Coitus ,Exercise ,Baby crying

Drugs

-- Dopamine antagonists

Antipsychotics (phenothiazines and butyrophenones

Antidepressants

Antiemetics (e.g. metoclopramide, domperidone

--Dopamine-depleting drugs

Reserpine ,Methyldopa

--Oestrogens

Oral contraceptive pill

Pathological

-- Disconnection hyperprolactinaemia (e.g. non-functioning pituitary macroadenoma

Prolactinoma (usually microadenoma

-Primary hypothyroidism--

-Polycystic ovarian syndrome

Macroprolactinaemia

- Hypothalamic disease

-Pituitary tumour secreting prolactin and growth hormone--------

Renal failure

Clinical assessment

--In women, in addition to galactorrhoea, the hypogonadism associated with hyperprolactinaemia causes secondary amenorrhoea and anovulation with infertility.

--In men there is decreased libido, reduced shaving frequency and lethargy.

- Important points in the history include drug use, recent pregnancy and menstrual history.

--Unilateral galactorrhoea may be confused with nipple discharge, and careful breast examination to exclude malignancy .or fibrocystic disease is important

Investigations

.

-The upper limit of normal for many assays of serum prolactin is 500 mU/l (14 ng/ml).

-In non-pregnant and non-lactating patients, prolactin concentrations of 500-1000 mU/l are likely to be induced by stress or drugs,

-Levels between 1000 and 5000 mU/l are likely to be due to either drugs, a microprolactinoma or 'disconnection' hyperprolactinaemia.

--Levels above 5000 mU/l are highly suggestive of a macroprolactinoma, and the higher the level, the bigger the tumour. Some macroprolactinomas cause .levels over 100 000 mU/l

-Patients with prolactin excess should have tests of gonadal function, and T4 and TSH

Management

-almost all cases of hyperprolactinaemia, dopamine agonist therapy will normalise prolactin levels with return of gonadal function.

-If gonadal function does not return despite effective lowering of prolactin, then there may be associated gonadotrophin deficiency or, in the female, the onset of the menopause.

Dopamine agonist drugs are

--Bromocriptine 2.5-15 mg/day 8-12hourly

Proven long-term efficacy

Ergotamine-like side-effects (nausea, headache, postural hypotension, constipation

Frequent dosing so poor compliance

--Cabergoline 250-1000 μg/week --

Long-acting, so missed doses less important.

have fewer ergotamine-like side-effects

ACROMEGALY

-Acromegaly is caused by growth hormone (GH) secretion from a pituitary tumour, usually a .macroadenoma

-If GH hypersecretion occurs before epiphyses have fused, then gigantism will result.

-More commonly, GH excess occurs in adult life, after epiphyseal closure, and acromegaly ensues.

-If hypersecretion starts in adolescence and persists into adult life, then the two conditions may be combined. ---
-The most common complaints are headache and sweating. -

Investigations

--The clinical diagnosis must be confirmed by measuring GH levels during an oral glucose tolerance test. In normal subjects, plasma GH suppresses to below 2 mU/l. In acromegaly, it does not suppress and in about 50% of patients there is a paradoxical rise.

--Prolactin concentrations are elevated in about 30% of patients due to co-secretion of prolactin from the tumour

--Additional tests in acromegaly may include screening for colonic neoplasms with colonoscopy

Management

--**Surgical**

Trans-sphenoidal surgery is usually the first line of treatment and may result in cure of .GH excess,

--**Radiotherapy**

External radiotherapy is usually employed as second-line treatment if acromegaly persists after surgery, to stop tumour growth and lower GH levels. However, GH .levels fall slowly (over many years) and there is a risk of hypopituitarism

--**Medical**

In patients with persisting acromegaly after surgery,

medical therapy to lower GH levels to < 5 mU/l.. Somatostatin analogues (e.g. octreotide or lanreotide) can be administered as slow-release injections every few weeks.

-A peptide GH receptor antagonist (-pegvisomant) is available for daily self-injection in patients whose GH concentrations fail to suppress following somatostatin analogue therapy