**Insulin Tolerance Test**

**Diagnosis or exclusion of ACTH and Growth Hormone Deficiency**

**Procedure:**

* Should only be performed in experienced specialist unit
* Exclude cardiovascular disease (ECG), Epilepsy or Unexplained blackouts
* Exclude severe untreated hypopituitarism (basal cortisol must be >100nmol/L; normal free T4)
* **Intravenous hydrocortisone & glucose** available for emergency
* Overnight fast, begin at 8 – 9am
* **Soluble insulin 0.15/kg, IV at time 0**
* **Glucose, Cortisol and GH levels at 0, 30, 45, 60, 90, 120mins**
* **Normal response**
	+ Cortisol rises >550nmol/L
	+ GH rises >7ng/L (severe deficiency = <3ng/L)
	+ Glucose rises must be <2.2mmol/L to achieve adequate stress response

**Symptoms and signs of hypopituitarism**

* **Secondary hypothyroidism** and **adrenal failure** both lead to **tiredness** and **general malaise**
* **Hypothyroidism:** BRADYCARIC + Opposite of THYROIDISME
* **Hypoadrenalism** causes **mild hypertension, hyponatraemia and ultimately cardiovascular collapse** and ultimately collapse during severe intercurrent stressful illness
* **Gonadotrophin** and thus gonadal deficiencies lead to loss of libido, loss of secondary hair, amenorrhoea and erectile dysfunction
* **Hyperprolactinaemia:** galactorrhoea and hypogonadism
* **GH deficiency** causes growth failure in children and impaired wellbeing in some adults
* **Weight may increase** in hypothyroidism or decrease in severe combined deficiency (pituitary cachexia)
* **Longstanding panhypopituitarism = PALLOR + HAIRLESSNESS**
* **Particular syndromes related to hypopituitarism**
	+ **Kallman’s syndrome**
		- Isolated GnRH deficiency
		- Mutations in the KAL1 gene
		- Recessive
		- Delayed puberty secondary to **hypogonadotrophic hypogonadism**
		- Characterised by **anosmia**
		- **LACK OF SMELL IN A BOY WITH DELAYED PUBERTY**
	+ **Septo-optic dysplasia**
		- Rare congenital syndrome presenting in childhood with a triad of **midbrain forebrain abnormalities , optic nerve hypoplasia and hypopituitarism**
	+ **Sheehan’s syndrome**
		- Due to pituitary infarction following **post partum haemorrhage**
	+ **Pituitary apoplexy**
		- Tumour occasionally **enlarges rapidly** owing to **infarction or haemorrhage**
		- Headache, double vision, sudden severe visual loss sometimes followed by acute life-threatening hypopituitarism
		- Often can be managed conservatively with the **replacement of hormones and close monitoring of vision**
		- If there is rapid deterioration in visual acuity and fields, surgical decompression of the optic chiasm may be necessary
	+ **Empty Sella Syndrome**
		- Defect in the diaphragm and extension of the subarachnoid space (cisternal herniation) or may follow spontaneous infarction or regression of a pituitary tumour
		- All or most of the sella turcica is devoid of apparent pituitary tissue but despite this pituitary function is usually normal, the pituitary eccentrically placed and flattened against floor/roof of fossa
* **Investigations**
	+ All hormones are measured in plasma
	+ **LH/FSH:** Oestradiol, Progesterone (day 21), Ovarian ultrasound, LHRH test
	+ **LH/FSH (Male):** Testosterone, sperm count, LHRH test
	+ **GH:** IGF-1, Insulin tolerance test, GH response to sleep, exercise or arginine
	+ All **FLATPG hormones**

**Anatomy**

* **Anterior pituitary (Adenohypophysis)**
	+ Arises from the oral ectoderm and forms **Rathke’s pouch**
	+ **FLATPG** released from this side (FSH, LH, ACTH, TSH, Prolactin, GH)
* **Posterior pituitary** is connected to the hypothalamus by the **infundibulum –** Produces Oxytocin + Vasopressin

**Tumours**

|  |  |  |
| --- | --- | --- |
| **Tumour or condition** | **Usual size** | **Common clinical presentation**  |
| **Prolactinoma**  | Most <10mm (micro) | Galactorrhoea, amenorrhoea, hypogonadism, erectile dysfunction  |
| Some >1mm (macro) | As above + headaches, visual field defects and hypopituitarism |
| **Acromegaly** | Few mm to several cm | Change in appearance, visual field defects and hypopituitarism |
| **Cushing’s disease** | Most are small: few mm | **CUSHINGOID** symptoms: Cataracts, Ulcers, Striae/bruising, Hypertension, Infection/irritability/insomnia, Necrosis of femoral head, Glycosuria, Oligomenorhoea/Osteoporosis, Immunosuppression, diabetes/depression |
| **Nelson’s syndrome** | Often large >10mm | **Post adrenalectomy, pigmentation, sometimes local symptoms. ACTH-pigmentation** |
| **Non functioning tumours** | Usually large >10mm | Visual field defects, hypopituitarism (microadenomas may be incidental) |
| **Craniopharyngioma** | Often large and very cystic | Headache, visual field defects (**lower quadrant defect > upper quadrant defect bitemporal hemianopia = superior chiasmal compression**), growth failure (50% occur below <20; 15% rise from within the sellar) |

**Infiltration of hypothalamic centres:** altered appetite, obesity, thirst, drowsiness/wakefulness

**Infiltration of the ventricles:** interruption of the CSF flow leading to hydrocephalus

**The sphenoid sinus** with invasion (erosion through the floor of the sella) causing CSF rhinorrhoea

**Investigations:**

* MRI
	+ Pituitary micro adenomas are very common (10% of normal individuals)
* Visual fields: Upper > lower bitemporal hemianopia = more common

**Acromegaly = Oral Glucose Tolerance Test /IGF-1**

**H** eart failure/hypertension
**O** edema
**T** eeth spaced widely
**A** ppearance/Amenorrhea/ poor libido
**C** arpal tunnel syndrome(pain/tingling in hands/course skin/voice)
**R** eek (sweaty)
**O** ily skin
**M** yopathy
**E** yes (prominent supra-orbital ridge)
**G** oiter/gain weight/galactorrhoea
**A** rthropathy
**L** arge tongue and nose
**Y** urinating a lot and thirsty
**Oral glucose test:** GH is suppressed to **<2mu/L** with **hyperglycaemia** in a NORMAL individuals. In acromegaly, there is **no suppression of GH.** May reveal impaired glucose tolerance associated with acromegaly. **IGF-1 = Diagnostic Investigation**
**Octreotide = somatostatin analogue** used in treatment (and also in TSH tumours)

**Hyperprolactinaemia
Milk production in the breast and inhibits GnRH 🡺** decreased libido, osteoporosis, delayed or arrested puberty, decreased facial hair, gynaecomastia **🡺 Cabergoline/Bromocriptine (dopamine agonist)
(HAGE: Hypogonadism, Amenorrhoea, Galactorrhoea, Erectile dysfunction)**

 **Diabetes Insipidus
Most common causes: hypothalamic-pituitary surgery (Desmopressin = Mx)**May be masked by **simultaneous cortisol deficiency
Symptoms and signs: polyuria, polydipsia, nocturia** 🡺 weakness, lethargy, irritability, confusion, coma, fits (DIURESIS = DEHYDRATION = HIGH SERUM SODIUM)
**Clinical features: deficiency of vasopressin (ADH) or insensitivity to it**
**Investigations:** U&E’s, Calcium levels, Glucose levels, **Urine:Serum osmolarity ratio,** if >**2:1** then diabetes insipidus is excluded (assuming plasma osmolality is <295mOsmol/kg), Imaging (MRI head for cranial DI – tumours)
**Biochemistry:
- increased or high-normal plasma osmolality** with **decreased urine osmolality**
- **hypernatremia
- increased 24h urine volumes
- failure of urine concentration with fluid deprivation
WATER DEPRIVATION TEST:** Diagnosis or exclusion of diabetes insipidus
- Fasting and no fluids from 0730 (or overnight)
- Monitor **serum and urine osmolality, urine volume and weigh h ourly** for up to **8hrs
-** Abandon fluid deprivation if weight loss 3% occurs
- If serum osmolality >300mOsm/kg and or urine osmolality <600mOsm/kg, give **desmopressin 2ug IM** at the end. **Normal response:** serum osmolality remains in the normal range, urine osmolality rises to >600
**Nephrogenic DI:** Desmopressin does not concentrate urine (causes inc: lithium, demeclocycline, hypokalaemia, hypercalcaemia) – **Tx**: **thiazide diuretics, NSAID, low salt + protein diet**
**Cranial DI:** Urine osmolality rises by >50% after desmopressin

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**Phaeochromocytoma**

**10% RULE : Features**

* 10% are multifocal, 10% are bilateral, 10% are extra-adrenal, 10% are malignant, 10% occur in children

Originates from the **neural crest tissue** that forms the **adrenal medulla, sympathetic chain** and **visceral autonomic tissue**

Most common active products are **catecholamines** but vasopressin, somatostatin, ACTH and oxytocin may also be secreted

Excess catecholamine secretion leads to characteristic episodes of:

* Headache, Sweating, Palpitations, Paroxysmal hypertension, Tachydysarrhythmias, Feeling of impending doom or death may also occur

Attacks can be triggered by activities causing mechanical pressure on the tumour e.g. physical exercise, defecation, intercourse, ingestion of alcohol, labour, general anaesthesia and surgical procedures

Only 50% of patients have persistent hypertension

**Investigations**

* **24 hour urine collection and assessment of metanephrines**
* **Clonidine suppression test –** failure of the urine levels to fall after dose
* **Thoraco-abdominal** **CT/MRI scanning** especially for adrenal and sympathetic chain tumours
* **MIBG scanning** localises extra-adrenal sites not seen on CT or MRI

**Treatment**

* Imperative to control BP prior to contemplating any surgical intervention
* **Alpha-blockade** (e.g. **Phenoxybenzamine 10mg bd/tds** up to the maximum dose tolerated) until the hypertension is controlled(**THIS FIRST)**
* **Beta-blockade** ( e.g. **propranolol)** can be added after hypertension controlled to control the beta-adrenergic effects (tachycardia)

**Surgical Treatment:**

* Laparoscopic adrenalectomy for smaller adrenal tumours (<8cm); open for larger tumours
* Local or radical excision is appropriate for extra-adrenal tumours

**Multiple Endocrine Neoplasia (AD)**

**MEN 1 (Chromosome 11)**

* **3 P’s and a C**
	+ **Parathyroid gland tumours:** by age 40, 95% of patients have hypercalcaemia
	+ **Pancreatic islet cell tumours:** insulin and gastrin = commonest
		- **Gastrinoma** leads to **Zollinger Ellison Syndrome (**recurrent and multiple peptic ulcers, severe reflux oesophagitis and diarrhoea **)**
		- Rarer tumours are **VIPoma, glucagonoma, somatostatinoma**
	+ **Anterior pituitary tumours**
		- Commonest is **prolactinoma**
		- Rarer: GH, ACTH tumours
* **Carcinoid tumours** (thymus, lung, foregut), adrenal tumours, lipomas and pinealomas have also been reported in MEN1 PATIENTS

**MEN 2A- Chromosome 10 RET oncogene (2P’s and a T)**

* **Medullary Thyroid Carcinoma**
	+ Originates in the **calcitonin-secreting parafollicular C-cells**
	+ Presents as unilateral or bilateral thyroid nodules with/without associated cervical lymphadenopathy
	+ Associated secretion of other peptides 🡺 severe diarrhoea
* **Phaeochromocytoma**
* **Primary Hyperparathyroidism**

**MEN 2B (2A + Marfinoid)**

* **Medullary Thyroid Carcinoma**
* **Phaeochromocytoma**
* **Marfinoid specific body habitus** (tall, slender, high arched palate and long extremities)



**Gynaecomastia**

**Causes:**

* Physiological, Syndromes with androgen deficiency: Kallman’s, Klinefelters, Testicular failure e.g. Mumps, Testicular cancer e.g. seminoma secreting HcG, Liver disease, Hyperthyroidism, Haemodialysis

**Drug causes:**

Digoxin, Finasteride, Goserelin, Oestrogens/anabolic steroids, cannabis, Cimetidine, Spironolactone, Tricyclics, Isoniazid, Calcium Channel Blockers, Heroin, Methyldopa.

**Causes of Increased Prolactin:** Metoclopramide(Dop antagonist), Prochlormethazine, Domperidone, Haloperidol.

**Dopamine Agonists = First line treatment for Prolactinomas i.e. Bromocriptine, Cabergoline**