**The hypothalamus & pituitary gland - Anatomy / physiology:**

The pituitary gland is enclosed in the sella turcica bridged over by the diaphragma sella, with the sphenoidal air sinuses below and the optic chiasma above. The cavernous sinuses are lateral to the pituitary fossa & contains the 3rd, 4th and 6th cranial nerves.

The gland is composed of two lobes anterior & posterior & 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 fibers to the posterior lobe. The anterior lobe comprising about 80% of the gland.

**The anterior lobe:**

This consists of three main types of cell by conventional staining, chromophobe, acidophil and basophil. The immunohistochemistry using specific antisera against the pituitary hormones is more valuable in identifying the hormone secreted by specific pituitary cells.

There are seven pituitary hormones, four of them act on target endocrine glands (ACTH, LH, FSH and TSH) & the other three act primarily on the target tissues (GH, Prolactin and LPH (β liporophin).

**Corticotrophin (ACTH)**

The secretion is under the control of CRF (corticotrophin releasing factor) & secreted as part of the large precursor molecule pro-opiocortin. ACTH release is affected by:

1. Circadian rhythm.
2. Stress.
3. Negative feedback.

**FSH in male:**

Stimulate sertoli cells in somniferous tubules to secrete androgen binding protein, transferrine, plasminogen activator & inhibin.

In female: FSH produces the follicular phase of menstrual cycle in which there is growth & development of ovarian follicles during the first 14 days of the cycle. This leads to gradual increases in Oestriadiol (E2) production. This increasing E2 level initially suppresses FSH secretion (negative feedback) but then results in increased LH secretion (positive feedback); this is due to an increase in both the frequency & amplitude of GnRH.

LH in male stimulates interstitial (Leydig) cells to produce testosterone. Both FSH & LH are necessary for spermatogenesis. In female the midcycle peak of LH (the LH surge) induces ovulation after release of the ovum the follicle differentiates into a corpus luteum which secretes progesterone, the second half of the cycle is known as the luteal phase.
**Inhibin:** It’s a glycoprotein hormone secreted by the ovaries & testes the major role is to suppress pituitary for FSH release.

**GH:**

It’s controlled by a dual system. GHRH & GHRIH or somatostatin, which inhibits other hormones such as Gastrin, TSH, Glucagon, gastric acid, insulin & pancreatic enzymes. The major effects of GH are mediated via an (IGF1) (Somatomedin C), which is mainly produced by the liver.

**Prolactin (PRL)**

Its secretion is differ from that of the others in that it’s under predominantly inhibitory control (Dopamine) which is secreted by the hypothalamus into the portal system.

**The posterior lobe (neurohypophysis):**

It contains neural fibers & secretes two hormones AVP (Arginine vasopressin) & Oxytocin. The principal action of AVP is to increases the reabsorption of water by the renal tubules & because of this action is known as ADH antidiuretic hormone. The role of oxytocin in the male is unknown. In the female its important is in parturition & the expression of milk from the breast.

**Diseases of anterior pituitary**

**Hypopituitarism:**

It refers to deficiency of one or more pituitary hormones.

**Aetiology:**

They are best classified on the bases of whether the lesion is in the hypothalamus or pituitary.

- **Hypothalamic causes**
  
  (A) Congenital
  
  - Gonadotropic releasing hormone (Kallmann syndrome) delayed puberty.
  - TRH→Hypothyroidism
  - GHRH→Short stature.
  - CRF→Adrenal insufficiency.

  (B) Acquired
  
  - Craniopharyngioma, germinoma, meningioma, glioma.
  - Inflammatory disease as granulomatous disease e.g. Sarcoidosis, T.B, Syphilis.

  Or Eosinophilic granuloma or histiocytosis-x relatively benign condition→pulmonary infiltration, usually in the 3rd & 4th decade of life, on CXR leads to honey comb lesion & pneumothorax sometime and should be differentiated from Sarcoidosis.

  Head injury, surgery, radiotherapy.

  Tumors-primary or secondary

- **Pituitary causes**

  Commonly pituitary adenoma (with or without infarction) or secondary tumor.

  Pituitary surgery, heavy particle pituitary irradiation by rods of yttrium.
Closed head trauma, head injury.

Postpartum necrosis (Sheehan's syndrome) this occurs because the enlarged pituitary gland of pregnancy becomes vulnerable to ischemia postpartum hemorrhage with systemic hypotension can destroy the pituitary gland. Normal pituitary gland weights 0.5-0.9gm& has the highest blood flow of any tissue in the body 0.8ml/gm/min.

Another cause of pituitary infarction is vascular disease as in diabetes mellitus or in sickle cell anemia.

Pituitary apoplexy hemorrhage or infarction in a pituitary macroadenoma with sudden increase in its size.

Autoimmune (lymphocytic hypophysitis) a syndrome usually occurs during pregnancy or in the postpartum period. it's often occurs with other autoimmune diseases such as Hashimotos thyroiditis& gastric atrophy, on CT scan there is a mass lesion on biopsy consists of lymphocytic infiltration.

Idiopathic.
Clinical features of hypopituitarism

These depend on the underlying lesion, in the congenital defects of the hypothalamus where there is an isolated failure of a releasing hormone (e.g. GnRH), Kallmann’s syndrome there is failure LH and FSH production and hence of gonadal steroids, the rest of hypothalamo-pituitary function is normal. There is however in these cases an important associated abnormality anosmia and midline anatomical defect.

Hypothalamic disorder may cause hypopituitarism with the exception that secretion of prolactin may be increased. Diabetes insipidus due to AVP deficiency is virtually diagnostic of hypothalamic disease or of high interruption of the pituitary stalk. Disturbance of thirst, temp regulation, appetite and blood pressure may occur with hypothalamic disorder as well.

Large hypothalamic mass may lead to visual field disturbance, obstruction of third ventricle and invasion of surrounding brain tissue. with progressive lesion of the Pituitary gland such as gradual expanding non-functioning pituitary tumor there is a characteristic sequence of loss of pituitary hormone secretion.

GH secretion is often the earliest to be lost but this produces no obvious symptoms in the adult except subtle manifestation such as fine wrinkling around the eyes and mouth and in subjects with diabetes mellitus increase sensitivity to insulin. But in children it leads to short stature.

Next LH secretions becomes impaired in the male leads to loss of libido and impotence, there may be gynaecomastia and decrease frequency of shaving, decrease beard .secondary sexual character in male (Beard, body hair and external genitalia) produced by androgen.

In female leads to oligomenorrhea or amenorrhea. In both sexes axillary and pubic hair eventually becomes sparse or even absent.the skin becomes characteristically fine and more wrinkled. FSH secretion tends to be lost later than LH. In case of Sheehan’s syndrome, inability to lactate is the most common initial clinical clue and other symptoms of hypopituitarism may unfold over months or year’s .the condition is some times diagnosed years after the primary events.

The next hormone to be lost is usually ACTH in contrast to primary adrenal insufficiency zona glomerulosa function is not lost and hence angiotensin II induced aldosteron secretion maintains normal plasma electrolyte ,also in contrast to the pigmentation of Addison’s disease a striking degree of pallor is usually present principally because of lack of melanin in the skin.

The features of cortisol deficiency are fatigue, decrease appetite, weight loss &hypotension. Children with combined GH&cortisol deficiency often develop hypoglycemia. Finally TSH secretion lost with consequent secondary hypothyroidism. This leads to fatigue apathy &cold intolerance, incontrast to primary hypothyroidism frank myxodema &goiter is not seen.deficiency of prolactin leads to failure of milk production which is of importance only to lactating women.

-Untreated sever hypopituitarism leads to coma; this may follow some mild infection or injury.
**Coma in Hypopituitarism:**

<table>
<thead>
<tr>
<th>Possible cause</th>
<th>measure</th>
<th>aetiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Hypoglycaemia</td>
<td>↓Blood glucose</td>
<td>lack of GH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \rightarrow \uparrow ) ins sensitivity</td>
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<tr>
<td>2- Water intoxication</td>
<td>Na↓, K↓</td>
<td>Cortisol require</td>
</tr>
<tr>
<td></td>
<td>Blood urea↓</td>
<td>for excretion of water load</td>
</tr>
<tr>
<td>3- Hypothermia</td>
<td>Rectal temp may</td>
<td>Hypothyroidism</td>
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**Investigations:**

1- **Basal function of anterior pituitary** by measuring plasma level of the following hormones by radio immunoassay.

- 08.00 h Cortisol
- Prolactin
- Thyroxine
- In the ♂ testosterone
- In the ♀ oestradiol
- In the post-menopausal ♀ LH/FSH.

2- **Assessment of G.H secretion.**

In normal subject sampled during the day G.H levels are commonly undetectable. In suspected hypopituitarism there for, some form of dynamic function test is necessary to distinguish normal from abnormal G.H secretion, the test are

   a. Post exercise
   b. 1 hour after going to sleep (physiological)
   c. Frequent sampling during sleep
   d. Insulin induced hypoglycemia
   e. clonidin
   f. Arginine (pharmacological)
   g. Glucagons

Insulin tolerance test remain the gold standard.it has additional advantage that stimulates secretion of ACTH & hence cortisol. It's contraindicated in conditions when hypoglycemia is dangerous as

   a. Ischemic heart disease.
   b. Epilepsy.
   c. Severe hypopituitarism when plasma cortisol at 08.00h <180nmol/L.

In the test 0.1-0.15u/kg body weight soluble insulin is given I.V the aim is to produce adequate hypoglycaemia (signs of neuroglycopenia-tachycardia&sweating-with blood glucose less than 40mg/100ml. Blood sample for glucose at 0, 30, 45, 60, 90 and 120 minutes are taken also plasma cortisol and GH is measured.

In normal subjects GH level rise to above 20mu/L and cortisol more than 550nmol/L. In sever GH deficiency levels are less than 7mu/L while partial GH deficiency produces intermediate value. Normal GH level is 0-3mu/L.

3- **TSH measurement.**

By giving TRH 200µg I.V, measure TSH & prolactin before & at 20 and 60 minute after. In Sheehan's syndrome the prolactin response is absent.
Management:
According to the deficiency demonstrated:

1. Cortisol replacement.
   This should be started if there is ACTH deficiency, in someone who is not critically ill, cortisol should be given by mouth. 20mg on waking & 10mg at 18:00h, excess weight gain indicate over replacement, persistant lethargy indicates inadequate dose, no need for mineralocorticoids.

2. Thyroid hormone replacement.
   If this is required then thyroxine 0.1 -0.15mg once daily should be given.it is dangerous to give thyroid replacement to patients with adrenal insufficiency without first giving glucocorticoid therapy.

3. Sex hormone replacement; Indication:
   a. Restore normal sexual function in gonadotrophin deficiency.
   b. To prevent osteoporosis.
   For male to restore sexual activity:
   - Depot testosterone ester(sustanon) 250-500mg i.m , every 2-4 weeks given, depends on symptoms and pcv every (6-12 months) or
   - Testosterone undecanuate 80-120mg oral twice daily 3-6 months.
   - Testosterone implant 600-800mg s.c. 3-6 months. Side effect is water retention.
   In premenopausal female the treatment is cyclical estrogen therapy, e.g. ethinyl estradiol 20-30µg daily for 3 week, with progesterone such as medroxy progesterone acetate (5 mg daily) for days 14-21. Ethinyl estradiol is contraindicated in severe liver dysfunction, jaundice, thromboembolic phenomenon and pregnancy.
   *Patients requiring fertility needs gonadotrophin therapy, by human chorionic gonadotrophin (hcG) 3000IU im weekly to stimulate testosterone production for the first 6 months, & then hCG weekly together with FSH usually as (pergonal) 75 IU im 3times/week, this combination should be continued for 9-12 mons. If there is a hypothalamic cause then a pulsatile GnRH therapy with a portable infusion pump may be effective.

   By daily SC self-inj ,to young patients with GH deficiency ,renal failure or Turner syndrome to assist them in attaining their growth potential .In adult GH improves quality of life ,exercise capacity ,lipid profile and body fat distribution ,although results are inconsistent between trials and between patients.
GROWTH HORMONE DEFICIENCY

Stature is polygenic trait. There is prenatal growth which depend on placental blood flow and parental growth which depends on nutrition and hormones (thyroxin, androgen, estrogen, GH which mediate its effect through ILGF1 (insulin like growth factor 1) or somatomedin c). Growth hormone deficiency leads to short stature, usually it is due to inability to secrete GHRH (growth hormone releasing hormone) rather than a primary pituitary abnormality. The next most common cause will be craniopharyngioma.

Accurate records of height and weight are kept & entered on a percentile chart, it is better to have serial measurements and measure growth velocity. If a child is below 3rd centile then careful serial measurements are necessary. The parental height should be noted. There is a clear relationship between the mid parental height & the expected height of the child, 95% of normal children will be within 8.5cm of the mid parental height.

Differential diagnosis of short stature:

1. Impaired growth velocity:
   A. Endocrine
      Isolated GH deficiency
      Panhypopituitarism
      Cushing syndrome
      Primary hypothyroidism
      Pseudohypoparathyroidism
   B. Abnormal body proportion
      Short limbs for spine (e.g. achondroplasia)
      Short limbs and very short spine (e.g. mucopolysaccharidosis)
   C. Other conditions
      Chromosome abnormalities (e.g. turner syndrome)
      Malabsorption (Coeliac disease, Crohn’s colitis)
      Systemic illness (asthma, heart and renal disease)
      Psychosocial deprivation

2. Normal growth velocity on presentation:
   Intrauterine growth retardation
   Congenital heart disease
   Constitutional short stature (normal bone age)
   Physiological growth delay (retarded bone age)

Diagnosis:

According to the age, height, and weight if there is low weight + short stature it is usually due to malnutrition or system illness. If there is overweight + short stature so endocrine disease e.g. Cushing syndrome, hypothyroidism, & GH deficiency are possibilities.
**Investigations:**
Serum thyroxin, bone age for constitutional delay & hypothyroidism are measured. ITT (insulin tolerance test) and IGF1 are measured which is decreased in short stature.

**Treatment of GH deficiency:**
In children with documented GH deficiency & impaired growth (biosynthetic GH 24 units/square meter/week divided into daily bedtime s.c injection). Patients with other causes of short stature such as turner’s syndrome may benefit from GH therapy.

**SYNDROMES OF ANTERIOR PITUITARY HYPERSECRETION**

**GIGANTISM AND ACROMEGALY**

Produced by pituitary macro-adenoma, Very rarely by ectopic GH secretion by pancreatic, breast and lung tumor. Ectopic GHRH can occur within pancreatic islet cell tumor.

**Gigantism:** GH hyper secretion before epiphyseal closure.

**Acromegaly:** more common and occur after epiphyseal closure in adult life.

If GH hyper secretion occur in adolescence and persists into adult life then both conditions may be combined.

**C/F of acromegaly:**

1. **Soft tissue changes:**
   There will be thickening of the skin, increase sweating, increased sebum production. Enlargement of the lips, nose and tongue. Increased heel pad thickness >18mm in female, >21 mm in male. Arthropathy, myopathy, carpal tunnel syndrome, parasthesia. Visceromegaly (e.g. thyroid, heart & liver) deepening of the voice, acanthosis nigricans.

2. **Acral enlargement (fingers and toes)**
   Large hands (difficult to remove rings). Large feet (Increase shoe size, increase width)

3. **Other bone changes**
   Prognathism- growth of lower jaw, other features are prominent supraorbital ridges with large frontal sinuses. Kyphosis

4. **Metabolic effects**
   Present in the form of glucose intolerance in 25% & diabetes mellitus in 10%, hypertriglyceridemia, hypertension, congestive heart failure. Other metabolic effect is increased GFR & reabsorption of phosphate

5. **Long term complications**
   Atheromatous disease, colonic cancer (2-3 folds relative risk)
   Other features due to pituitary tumor are headache, visual field defect. Cranial nerve palsy. In 30% of patients they have increased prolactin level also.
The tissue effects of raised GH lead to high circulatory level of insulin like growth factor 1 (IGF1).

Radiographic investigations: on skull x-ray there is thickening of skull + increase bone density.

**Treatment:**

1. **Surgical with radiotherapy:**
   Trans-sphenoidal surgery may lead to selective removal of an adenoma with cure of GH excess especially in patients with microadenoma.

2. **Radiotherapy:**
   But it will lead to slowly decrease in GH while 35% will develop hypopituitarism.

3. **Medical:**
   It is used in patient with persisting acromegaly after surgery the aim is to lower GH level to below 5 mU/l which is associated with normal survival. In patient who had received radiotherapy medical therapy may be discontinued after several years somatostatin analogus e.g. Octreotide or lanreotide can be administered i.m slow release injection every few wks, octeriotied doesn't reliably shrink the tumor.

   Side effect: abdominal cramps, cholelithiasis & tempory steatorrhoea. bromocreptine are less potent, in lowering GH but may be helpful especially in patients associated with prolactine excess, it ↓ GH in 75% of patients starting by small dose 1.25-2.5 mg/day & gradually ↑ to 20-30 mg/day.

   Encouraging trails have also been performed with GH receptor antagonist e.g Pegvisomant which is used when you have not had an adequate response to other treatments(e.g.,surgery, radiation) it helps decrease the blood levels of IGF1 and other related proteins ,i.e injected subcutaneously usually once daily and the maximum regular daily dose should not exceed 30 milligrams, side effects are pain/redness/itching at the injection site, diarrhea or nausea may occur.

**Response to treatment**

In pts with successful reduction in GH there is cessation of bone overgrowth with clinical improvement in reduction of soft tissue bulk of the extremities ↓ facial puffier, ↑ energy & cessation of hyperhidrosis, heat intolerance & oily skin headache, carpal tunnel syndrome, arthralgia are also reversible with successful therapy. Glucose intolerance and hyperinsulinemia also reversed in most cases, the excess mortality is reversed if GH levels are normalized.

**HYPERPROLACTINAEMIA:**

Elevation of prolactin level is a common endocrine finding, careful history especially with regards to drug therapy may rapidly reach a presumptive diagnosis.
Causes of elevated plasma prolactin:

1. Physiological:
   Stress, pregnancy, lactation.

2. Drugs:
   Dopamine antagonists,
   Phenothiazine e.g. chlorpromazine
   Butyrophenone e.g. haloperidol
   Antiemetics (e.g. metoclopramide, domperidone)
   Dopamine depleting drugs e.g. reserpine, methyldopa.
   Estrogen
   TRH
   H2 receptor blockers

3. Pathological:
   a. Common:
      Disconnection hyperprolactinaemia e.g. (nonfunctioning pituitary tumor)
      prolactinoma
   b. Uncommon:
      Hypothalamic disease
      Mixed pituitary tumor
      Renal failure
   c. Rare:
      Chest wall reflex e.g. nipple stimulation
      Post herpes zoster
      Ectopic source

C/F:
May be associated with galactorrhoea (milk production in a patient who is not postpartum present in 30-90% of hyperprolactinaemic women) and therefore; the breasts in both sexes must be examined.

In female amenorrhea, oligomenorrhea, deficient luteal phase progesterone production or menorrhagia may all be associated with hyperprolactinaemia. It is important to measure prolactin in cases of unexplained infertility. In male, it usually presents with loss of libido or impotence, and at this stage many have a macroadenoma often with associated visual field defect.

Investigation:
Plasma prolactin level >4000 mU/L almost invariably indicate a diagnosis of prolactinoma. (upper limit of normal 360 mU/L). Because of variation with stress of venipuncture it is useful to have more than one basal prolactin level.
Management:

1. Medical:
In almost all cases of hyperprolactinaemia dopamine agonist therapy (bromocriptine) will lower prolactin levels often to below normal with return to gonadal function (regular period and fertility in women, return of libido & potency in male). The usual dose is 2.5 mg orally 3 times daily with meals. As with acromegaly the drug must be started at a low dose 1.25 mg/day and gradually increased. Cabergoline has actions and uses similar to those of bromocriptine but its duration of action is longer. Patient intolerant to bromocriptine may be able to tolerate cabergoline, dose 500µg weekly as a single dose or as two divided doses on separate days, increase as monthly interval optimal range 0.25-2mg/week. If gonadal function does not return despite effective lowering of prolactin, then there may be associated gonadotrophin deficiency or in the onset of a premature or normal menopause.

2. Surgical:
Bromocriptine not only lowers prolactin levels but shrinks the majority of prolactin-secreting macroadenomas, thus surgical removal of these large tumors is not usually necessary unless they are cystic.

However microadenomas can be removed selectively by trans-sphenoidal surgery with a cure rate of about 80% and it is successful by low incidence of hypopituitarism.

3. Radiotherapy:
External irradiation as definitive treatment for some macroadenomas to prevent re-growth if bromocriptine is stopped but incidence of hypopituitarism is more than surgery.

Pregnancy
Prolactinoma may enlarge rapidly during pregnancy & thus these patients need careful assessment prior to becoming pregnant & supervision with assessment of prolactin levels & visual fields during pregnancy.
PITUITARY TUMORS

Aetiology:
These tumors are monoclonal & they arise from a somatic mutation in a single cell. In up to 40% of GH secreting pituitary tumors there is a mutation in the gene for the α-subunit of the adenyl cyclase stimulating G protein (Gs) which is then converted into an oncogen.

Pathology
Anterior pituitary consists of three main types of cells by conventional staining.
- Chromophobe.
- Acidophil, leads to GH or prolactin excess microadenoma >10 mm
- Basophil, leads to ACTH hypersecretion microadenoma < 10mm.

By immunohistochemistry using specific antisera against the pituitary hormone is more valuable in identifying the hormones secreted by specific pituitary cells.

Prolactinoma: are prolactin secreting tumors are the most common of the pituitary adenoma, may be acidophil or chromophobe.

Craniopharyngioma are tumors which are usually cystic, commonly has suprasellar calcification.

Primary carcinoma of the pituitary is rare but metastatic tumor from a primary in the breast, lung, kidney or else where may occur in the hypothalamus and reduce pituitary function. Other tumors are epindymoma, meningioma. Conditions such as sarcoidosis, syphilis may mimic pituitary tumor.

C/F:
Depends on type of lesion in the pituitary and effect of it on surrounding structures, headache is the most constant but least specific symptom, and is mostly due to involvement of dura matter. Impaired visual field due to optic nerve, optic chiasma and optic tract compression could occur. Bitemporal hemianopia is the most characteristic finding associated with pressure on chiasma, Optic atrophy may be present. Diplopia and strabismus duo to 3rd, 4th and 6th cranial nerve compression could occur.

Tumor expansion sufficiently interfere with ADH secretion and leads to diabetes insipidus which indicates a suprasellar extension. Both micro and macroadenoma could be functional or nonfunctional. e.g.

GH excess leads to acromegaly / gigantism.
Prolactin leads to galactorrhea, menstrual dysfunction, impotence.
TSH leads to hyperthyroidism
ACTH leads to Cushing syndrome.

Tumors which expand upward to impinje on the hypothalamus may cause obesity, disturbance of sleep, thirst, temperature count, and appetite.

Investigation:
Anatomical and radiological investigation:
1. Plain x-ray
x-rays of pituitary fossa may demonstrate enlargement of sell turcica with clinoid process erosion, suprasellar calcification may be seen in a craniopharyngioma. A (double floor) of the sella may be present if the tumor enlarges the fossa asymmetrically.

A condition called empty sella, in which the sella tends to be symmetrically ballooned without bony erosion. In this condition the suprasellar subarachnoid space herniated through an incomplete diaphragma sella so that the sella is filled with CSF within an arachnoid lined sac and CSF pressure is usually normal in these patients, the pituitary is flattened & pushed to one side but tends to function normally, most patients with primary empty sella syndrome are obese multiparous women with headache, about 30% has hypertension. Therapy of patient with empty sella is by reassurance.

2. CT-scanning.
3. Cysternography(metrizamide).
4. MRI.
It is the imaging procedure of choice for hypothalamo pituitary lesions. Lesions as small as 3-5mm can be visualized by MRI performed in both sagital and coronal plains at 1.5-2mm intervals.

5. Visual field examination.
Other investigation includes assessment of function of anterior and posterior pituitary.

**Treatment:**

For prolactinoma, bromocriptine started with small dose 1.25mg/day and gradually increased. The tumor will shrink in 80% but if the drug stopped so the tumor re enlarge rapidly so many patient given definitive treatment with external radiotherapy.

If there is evidence of pressure on the visual pathway or there is nonfunctional tumor with visual field defect so surgery by trans sphenoidal approach and external radiotherapy after surgery is given.

In Cushing disease , prolactinoma and acromaegaly it may be possible selectively to remove adenoma.Other way of therapy is by external-radiotherapy to suppress tumor growth. Yttrium implantation in the pituitary fossa and proton beam therapy are other ways of therapy.

**Craniopharyngioma:**

They are benign tumors which develops in cell rests of Rathke`s pouch and may be located within the sella turcica, or commonly in the suprasellar space.

They are often cystic and/ or calcified, more common in young people, may present with pressure on pituitary or hypothalamic region.

Treatment: surgery by craniotomy, unfortunately recurr requiring repeated surgery and radiotherapy should probably be given, morbidity is high usually from hypothalamic obesity and/ or visual failure.

**POSTERIOR PITUITARY DISORDERS**

Posterior pituitary is axonal extension of hypothalamus from supraoptic and paraventricular area. Oxytocin leads to milk release and promote uterine contraction during labor.

Vasopressin leads to regulation of water metabolism, deficiency of ADH leads to diabetes insipidus, excessive and physiologically inappropriate secretion of ADH leads to hyponatraemia(SIADH).

**Diabetes insipidus**

It is uncommon disease characterized by the persistent excretion of excessive quantities of dilute urine and by constant thirst, divided to:

1. Cranial: deficient production of ADH.
2. Nephrogenic renal tubules unresponsive to vasopressin.

**Causes of cranial diabetes insipidus(DI)**

A: genetic defect: may be dominant or recessive as in (DIDMOAD) syndrome.

(Diabetes insipidus, diabetes mellitus, optic atrophy and deafness)

B: hypothalamic or high stalk lesion e.g. histeocytosis-X, sarcoidosis, craniopharyngioma, pituitary tumor with supra sellar extension, basal meningitis, head injury, surgery, encephalitis.

C: idiopathic.

**Causes of nephrogenic D I**

1. Genetic : X-linked recessive e.g. cystinosis.
2. Metabolic abnormality e. g. hypokalemia, hypercalcemia.
3. Drug therapy:
   A: lithium
   B: D-methyl chlortetracycline
4. Poisoning, heavy metals.

If there is associated cortisol deficiency then DI may not be manifested until glucocorticoid therapy is given.

**C/F:**

Polyuria and polydipsia , normal urine is 800-2500 ml/ 24hour, in these cases the patient may pass 5-20 L/24 hour. And it is of very low specific gravity and osmolality, in the
unconscious patient or one with damage to hypothalamic thirst centre, DI is potentially lethal unless the condition is recognized & appropriate therapy is given.

**Investigation:**

Water deprivation test:

No coffee, tea or smoking on the test day, free fluid until 07:30 hour on the morning of the test. No fluid from 07:30 hour.

Attend at 08:30 hrs for body weight, plasma & urine osmolality. Record body weight, urine volume, urine and plasma osmolality every 2hrs for up to 8 hrs.

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

If plasma osmolality reaches >300 mosm/kg & urine osmolality < 660mosm/kg this confirm DI then administer DDAVP 2µgm i.m and then collect urine hourly for further 4 hours.

Other investigation: skull x-ray, CT- scan, electrolyte, Calcium ion, and urinary tract investigation.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>DI (cranial)</th>
<th>DI (nephrogenic)</th>
<th>Psychogenic polydipsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine osmolality</td>
<td>800 mosm/kg</td>
<td>&lt;300 mosm/kg</td>
<td>&lt;300 mosm/kg</td>
<td>Low also but Plasma osmolality also is low</td>
</tr>
<tr>
<td>Vasopressin injection</td>
<td>No change</td>
<td>↑ &gt;9%</td>
<td>No response</td>
<td>Impaired</td>
</tr>
</tbody>
</table>

**Management:**

Cranial DI with des-amino-des-aspartate-arginine vasopressin(desmopressin or DDAVP) either intranasally as spray or using a manual aerosol device. In sick patient it is given by im injection the ideal dose to prevents nocturia but allow a degree of polyuria from time to time before the next dose. e.g. DDAVP nasal dose 5µgm in the morning and 10 µgm in the night. S/E: water intoxication and hyponatremia.

Nephrogenic DI is improved by thiazide diuretic e.g. bendroflumethiazide 2.5-5mg/day, amiloride (5-10mg/day) and indomethacin 15mg 8 hourly.

**SIADH (Syndrome of Inappropriate ADH Secretion):**

**Aetiology:**

Neoplasm: CA lung( small cell), pancreas, duodenum, ureter, bladder, prostate, lymphoma.

CNS disorder: meningitis, encephalitis, brain abscess, head injury, cerebral tumor, cerebrovascular accident, Guillain-Barre syndrome.

Non malignant: -pulmonary lesion e.g. pneumonia (bacterial & viral)

-drugs: narcotics, phenothiazine, tricyclic antidepressants, Vincristin, chlorpropamide, NSAID.

Miscellaneous: pain, postoperative period.

**C/F:**

It will lead to water excess, symptoms of cerebral function disorder, due to cerebral edema include dizziness headache, anorexia, nausea, and vomiting, mental confusion, severe water intoxication can cause convulsion, coma & death.

**Diagnosis:**

Plasma sodium below 130 mmol/L

Low plasma osmolality(<270mmol/kg)

Urine osmolality < 100 mosm/kg

**Management:**

Treat underlying cause. Water restriction; 400ml/day + urine output volume.

In severely symptomatic case 100ml 5% NaCl IV repeated in a few hours.

Treatment of tumor producing ADH is by D-methyl chlortetracycline 300mg 4 times daily. To inhibit action of the peptide on the collecting duct, the drug is nephrotoxic, it also commonly produce photosensitive dermatitis and patients must avoid direct sun light, the principal hazard is excessive treatment resulting in water intoxication & hyponatremia.

In persistent hyponatremia oral urea therapy and if available oral vasopressin receptor antagonists(vaptans)may be used.