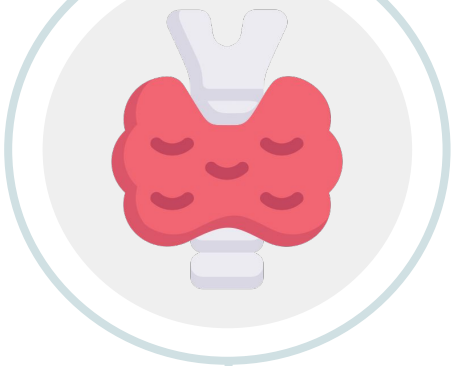
Pituitary disorders



Objectives :

- ★ **Anatomy of hypothalamus and pituitary**
- ★ **□ Function of hypothalamus and pituitary □**
- ★ **Hormones: □**
  - **Anteriorpituitary with related disorders**
  - **Posterior pituitary with related disorders**

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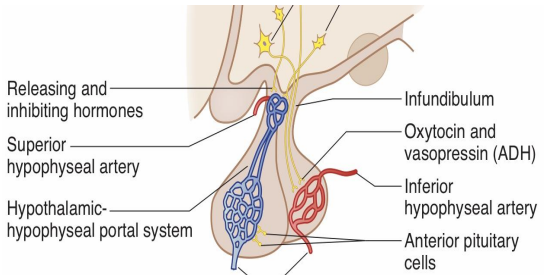
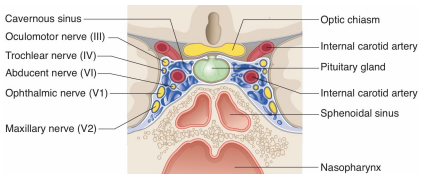
Review of the basics

◀ Anatomy of pituitary gland

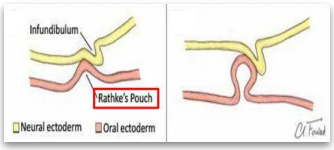




- Pituitary gland measures 15 X 10 X 6 mm, weighs 500 mg but about 1 g in women □
- Lies at the base of the skull as sella turcica
- The gland is composed of **two lobes**, anterior and posterior, and is connected to the hypothalamus by the **infundibular stalk** **(Pituitary stalk)** below the 3rd ventricle. Infundibular stalk has portal vessels carrying blood from the median eminence of the hypothalamus to the anterior lobe **(hypophyseal portal system)** and Axons of supraoptic & paraventricular cells to the posterior lobe **(hypothalamo-hypophyseal tract)**.
- Pituitary stalk in midline joins the pituitary gland with hypothalamus that is below 3rd ventricle
- Development of pituitary cells is controlled by a set of transcription growth factors like Pit-1, Prop-1, Pitx2
- Blood supply: superior, middle,inferior hypophysial arteries (internal carotid artery) running in median eminence from hypothalamus □
- Venous drainage: to superior and inferior petrosal sinsuses to jugular vein

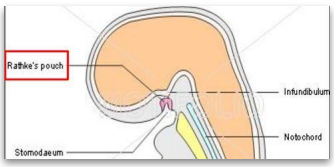
◀ Pituitary Development and Relations:

- Anterior pituitary is recognizable by 4- 5th wk of gestation □
- Full maturation by 20th wk □



- Portion of Rathke's spouch → Intermediate lobe □
- Remnant of Rathke's pouch cell in oral cavity → pharyngeal pituitary □

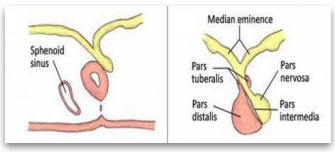
1



2

- From Rathke's pouch, Ectodermal evagination of oropharynx □
- Migrate to join neurohypophysis □

3



Anterior

Optic chiasm lies 10 mm above the gland and anterior to the stalk □

Lateral

The lateral wall surrounded by two cavernous sinus containing III, IV, VI, V1, V2 cranial nerves and internal carotid artery with sympathetic fibers. Both adjacent to temporal lobes □

Floor

by the roof of sphenoid sinus (Extension of a pituitary adenoma into the sphenoidal air sinus might lead to leakage of CSF through the nose, patient present with clear discharge from the nose (CSF rhinorrhea)). A transsphenoidal approach is used by surgeons when operating in the pituitary

Roof

- formed by diaphragma sellae
- Pituitary stalk and its blood vessels pass through the diaphragm □

- Pituitary and hypothalamic space-occupying lesions, (whether it is hormonally active or not) can cause symptoms **by pressure on, or infiltration of** The visual pathways[2], cavernous sinus[3], bony structures (causing headache) and hypothalamic centers[4]

1- if a pituitary adenoma compresses the temporal lobe, may lead to seizures
2- field defects and visual loss (most common, bitemporal hemianopia)
3- Outpouching of pituitary adenoma laterally into the cavernous sinus will put a pressure on the cranial nerves causing might lead to cranial nerve palsy (patient present with ptosis and numbness)
4- altered appetite, obesity, thirst, somnolence/wakefulness or precocious puberty

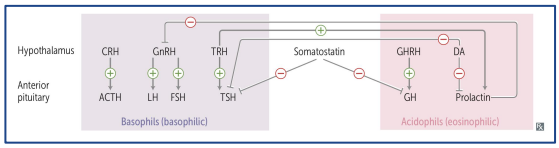
Review of the basics *cont.*

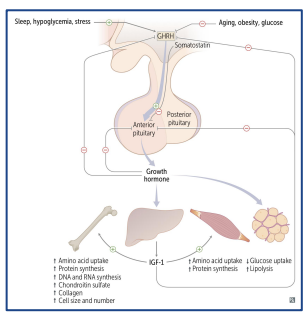
◀ Lobes of the pituitary

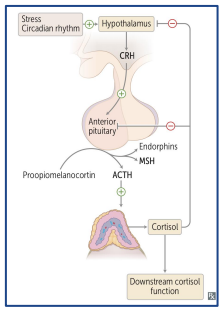
	Anterior (Adenohypophysis)[1]	Posterior (Neurohypophysis)
Origin	**Rathke's pouch** (Ectodermal evagination of oropharynx)[2]. Recognizable by 4- 5th wk of gestation and full maturation by 20th wk. Portion of Rathke's pouch→ Intermediate lobe	**Down growth of hypothalamic neural tissue** (as a 2 outpouching from the floor of 3rd ventricle)
Hormones released	**GH , LH, FSH, TSH, ACTH, Prolactin** (**G**o **L**ook **F**or **T**he **A**denoma **P**lease) *A compressive adenoma in will impair hormone production in this order	**Oxytocin, ADH**
Hormones synthesis	Hormones are **Synthesized** and Secreted in anterior pituitary.	Synthesized in the hypothalamus and **Stored** in the posterior pituitary.
Arterial supply (Internal carotid)	**Superior** hypophyseal	**Inferior** hypophyseal
Venous drainage	hypophyseal veins drain into cavernous sinuses, To superior and inferior petrosal sinuses to jugular vein.	
Hypothalamic control	Hormonal signals (releasing and inhibitory Neural signals control hormones)	Neural signals

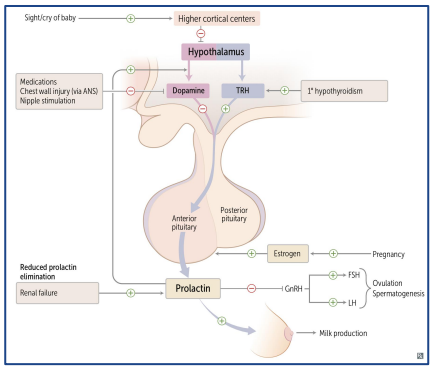
Hypothalamic-pituitary hormones

HORMONE	FUNCTION	CLINICAL NOTES
ADH	↑ water permeability of distal convoluted tubule and collecting duct cells in kidney to ↑ water reabsorption	Stimulus for secretion is ↑ plasma osmolality, except in SIADH, in which ADH is elevated despite ↓ plasma osmolality
CRH	↑ ACTH, MSH, β-endorphin	↓ in chronic exogenous steroid use
Dopamine	↓ prolactin, TSH	Also called prolactin-inhibiting factor Dopamine antagonists (eg, antipsychotics) can cause galactorrhea due to hyperprolactinemia
GHRH	↑ GH	Analog (tesamorelin) used to treat HIV-associated lipodystrophy
GnRH	↑ FSH, LH	Suppressed by hyperprolactinemia Tonic GnRH analog (eg, leuprolide) suppresses hypothalamic–pituitary–gonadal axis. Pulsatile GnRH leads to puberty, fertility
MSH	↑ melanogenesis by melanocytes	Causes hyperpigmentation in Cushing disease, as MSH and ACTH share the same precursor molecule, proopiomelanocortin
Oxytocin	Causes uterine contractions during labor. Responsible for milk letdown reflex in response to suckling.	Modulates fear, anxiety, social bonding, mood, and depression
Prolactin	↓ GnRH Stimulates lactogenesis.	Pituitary prolactinoma → amenorrhea, osteoporosis, hypogonadism, galactorrhea Breastfeeding → ↑ prolactin → ↓ GnRH → delayed postpartum ovulation (natural contraception)
Somatostatin	↓ GH, TSH	Also called growth hormone inhibiting hormone (GHIH) Analogs used to treat acromegaly
TRH	↑ TSH, prolactin	↑ TRH (eg, in 1°/2° hypothyroidism) may increase prolactin secretion → galactorrhea









For more details regarding anterior pituitary hormones Stimulus,Inhibitors and their trophic effect click **HERE**

1-The majority of anterior pituitary hormones are under predominantly positive control by the hypothalamic releasing hormones; the exception is prolactin, which is under tonic inhibition by dopamine.

2- In some rare conditions the pituitary does not fully ascend during embryological development, some remnants stay in the oropharynx (oropharyngeal pituitary/double pituitary) an ectopic/pharyngeal pituitary may be found

Review of the basics *cont.*

◀ Hypothalamus

- The hypothalamus is the coordinator of Endocrine system. The master organ that controls most of the endocrine glands. Pancreas and parathyroid gland, are not under the control of the hypothalamus.
- It receives signals from cortical brain, autonomic function, environment cues like light and temp.
- It affects function of thyroid gland, adrenal, gonads, growth, milk production and water balance.
- It has **Non-endocrine functions** such as: **temperature regulation**, **regulate the activity of the autonomic nervous system**, **control of appetite**.
- Multiple nuclei in anterior part producing hormones to anterior pituitary
- Paraventricular and supraoptic nuclei produce ADH to control poster pituitary function

Anatomy:

- At the base of the brain, below thric ventricle, above pituitary gland and optic chiasm
- Hypothalamus is connected to the pituitary gland by pituitary stalk which connect median eminence to the pituitary gland

Function:

- Terminals of hypothalamic neurons are in the median eminence carrying the hormones through capillary plexus to the pituitary gland.
- Release all the hormones to control the pituitary function beside neuroendocrine function
- Paraventricular and supraoptic nuclei produce ADH to control posterior pituitary function (Very important for survival)

◀ Hypothalamic-Pituitary Hormones ★

	Hypothalamic hormones	Pituitary hormones
Stimulatory	**CRH** - 41 amino acids; released from **paraventricular** neurons as well as **supraoptic** and **arcuate nuclei** and **limbic system**	**ACTH** - basophilic corticotrophs represent 20 percent of cells in anterior pituitary; ACTH is product of **proopiomelanocortin (POMC) gene**[1]
	GHrH - two forms, 40 and 44 amino acids	**GH** - acidophilic somatotrophs represent 50 percent of cells in anterior pituitary
	GnrH - 10 amino acids; mostly released from **preoptic neurons**	**LH and FSH** - gonadotrophs represent about 15 percent of anterior pituitary cells
	TRH - three amino acids; released from **anterior hypothalamic area**	**TSH**[2] - thyrotropes represent about five percent of anterior pituitary cells
	Prolactin-releasing factors - include serotonin, acetylcholine, opiates, and estrogens	**Prolactin** - lactotrophs represent 10 to 30 percent of anterior pituitary cells
Inhibitory	**Somatostatin** - 14 amino acids	**Inhibits the release of growth hormone**
	Prolactin-inhibiting factors - includes dopamine	**Major prolactin control is inhibitory**

1- POMC is a prohormone that gives rise to several biologically active peptides that are expressed primarily in the pituitary and brain. ACTH, the melanotropins, and endorphins. As they from the same precursor, ACTH can act directly on the melanocyte to enhance melanogenesis, which explains hyperpigmentation in cushing disease.

2- If the T4, T3 is low, and the TSH is high, where is the problem? Thyroid. But is the TSH is also low? Pituitary, or Hypothalamus.

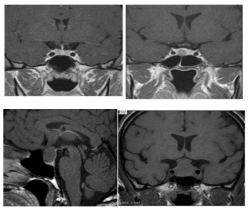
Pituitary Masses

◀ Etiology of Pituitary-Hypothalamic Lesions

1 Tumours

- Anterior Pituitary
  - Hormone excess
    - Hyperprolactinemia (Prolactinoma)
    - Acromegaly (GH Adenoma)
    - Cushing disease (ACTH adenoma)
    - hyperthyroidism (Thyrotropinoma)
    - Other mixed endocrine active adenomas
  - Hormone deficiency
    - Central hypoadrenalism, hypogonadism, hypothyroidism or GH deficiency, Panhypopituitarism (≥3 hormone affected), Sheehan syndrome
- Posterior Pituitary
  - Hormone excess
    - Syndrome of inappropriate antidiuretic hormone (SIADH)
  - Hormone deficiency
    - Central diabetes insipidus

2 Pituitary cyst



- Rathke's cleft cyst
- Mucoceles

3 Non-Functioning tumours[3]

- They affect hormones release indirectly by comprising parts of the pituitary glands

4 Miscellaneous

- Empty sella syndrome[1]
- Pituitary abscess: e.g. **TB**
- Carotid aneurysm[2]
- Malignant pituitary tumors[5]: Functional and non-functional pituitary carcinoma
- **Lymphocytic hypophysitis** (antibodies attacking the pituitary)
- sarcoidosis
- Metastases in the pituitary (breast, lung, stomach, kidney)

◀ Evaluation of Pituitary Masses

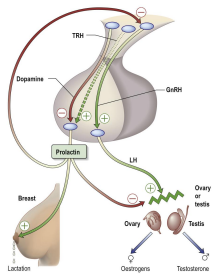
	Functional adenoma	Non-functional adenoma (incidentaloma)
Epidemiology	10 % of all pituitary lesions • Genetically-related to MEN-1, Gs-alpha mutation, PTTG gene, FGF receptor-4)	1.5 -31% in autopsy (prevalence) 10% by MRI most of them < 1 cm
Clinical (History and Examination)	• Function (oversecretion or hyposecretion) • Mass (headache,visual symptoms) • Most exclusively proliferate in only one type of endocrine cell and therefore secrete only one pituitary hormone.	• **Asymptomatic** • Incidentaloma by imaging. • Mass-effect (Bitemporal hemianopia) • Gonadal hypersecretion
Biochemical	Screen Test, Confirmatory Test	**GH, LH, FSH, TSH, ACTH:** not high. **PRL could be:** low, high or normal.
Anatomy	**MRI** of sella turcica (MRI is superior to CT)	
Treatment	• Surgical >Medical >Radiation or Medical >Surgical >Radiation (Depend on the type)	• Surgery if indicated • Observation • Adjunctive therapy[4]

1- An 'empty sella' is sometimes reported on pituitary imaging. This is sometimes due to a defect in the diaphragma and extension of the subarachnoid space (cisternal herniation), or may follow spontaneous infarction or regression of a pituitary tumour.
2- May masquerade as pituitary tumours and must be diagnosed before surgery.
3- Most intrasellar tumours are pituitary macroadenomas (most commonly non-functioning adenomas), whereas suprasellar masses may be craniopharyngiomas. The most common cause of a parasellar mass is a meningioma.
4- eg: Radiation therapy, Dopamine agonist, Somatostatin analogue.
5- they are aggressive, invades the bone

1- Hyperprolactinemia

◀ Introduction

- **Function of prolactin:** Stimulates **milk production** in breast; **inhibits ovulation** in females and **spermatogenesis** in males by **inhibiting GnRH** synthesis and release. Therefore, lactating can be used as a natural way for contraception.
- **Regulation of prolactin:** Prolactin release is under tonic **inhibition by dopamine** from the hypothalamus and factors that increase prolactin secretion (e.g. **TRH**) are probably of less relevance. There is a physiological increase in serum prolactin during pregnancy, lactation and severe stress.
- **Prolactinomas are the most common of functional pituitary adenomas**
- **25-30%** of all pituitary adenomas
- Some **GH-producing tumors also co-secrete PRL** (and vice versa).
- PRL is the only pituitary hormone that is **inhibited by hypothalamus**
- Prolactinomas lose TRH response



◀ Causes of Hyperprolactinemia

Pathological

- The most common cause is a **prolactin secreting pituitary adenoma (prolactinoma)**.
- Disruption of dopamine (tumor,trauma, infiltrative lesions)
- Other causes are **Renal failure** (returns to normal after transplant), **Liver failure**, **primary hypothyroidism** (high TRH levels stimulate prolactin).
- ★ Drugs which interfere with dopamine:(**Phenothiazines, Domapine receptor antagonists metoclopramide, a-methyldopa, verapamil, H2 blocker, estrogen, opiates, reserpine**).

Physiological

- **Mildly increased serum prolactin levels may be physiological and asymptomatic, could be due to:**
  1. Asleep, stress
  2. Pregnancy (Estrogen increases, most common)
  3. Lactation
  4. Chest wall stimulation (Burns, chest wall surgery) causing neuronal effect like suckling
  5. Trauma.

◀ Clinical features

	premenopausal women	Males
↑ Prolactin	Galactorrhoea (nipple discharge)	Gynecomastia & galactorrhoea (Rare)
↓ LH + ↓ FSH	Oligo or amenorrhoe & Infertility	-
↓ Testosterone	Loss of libido	○ Decreased libido, subfertility, erectile dysfunction
Presentations of prolactinoma	90% present with **Microprolactinomas** (<10mm) Because in a female, minor elevations in prolactin lead to disturbance of their menstrual cycle, leading them to seek medical attention early	60% present with **Macroprolactinomas** (>10mm) Because in males, no symptoms appear until the adenoma grows in size and start causing problems such as decreased libido and ED.
	It may have mass effect → Bitemporal hemianopia ◐◑	

1- Hyperprolactinemia *cont.*

◀ Investigations

Note: When you have elevated prolactin, do not jump into thinking of adenoma, always consider other factors first (drugs, surgeries of chest wall, pregnancy)

- **Biochemical (hormonal):**
  - **Serum prolactin level:** At least 3 measurements should be taken, **Very high** level suggests prolactinoma (>5000mU/L).
  - **Pituitary hormones:** GH, LH, FSH, TSH, ACTH: **normal or low**.
  - **Thyroid function test: TSH** must be tested to rule out primary Hypothyroidism.
  - **IGF-1** must be tested to rule out acromegaly co-secretion.
  - **Pregnancy test:** Always exclude pregnancy first
  - Also check LFT and RFT, because renal and liver failure may cause elevated prolactin
- **Anatomical (Imaging):**
  - CT or **MRI** of the pituitary .
  - < 1 cm (microadenoma), > 1cm (macroadenoma)
- **Others:** Visual fields (clinical assessment and perimetry)

◀ Treatment

- **Treat only if symptomatic (hormonal abnormality, vision changes)**

1 Medical (First line)

- **Dopamine agonist drugs** (e.g. Bromocriptine,**Cabergoline (Drug of choice)**, Quinagolide) **are first-line** therapy for the majority of patients especially in those with macroprolactinomas. However, it is not recommended for breastfeeding moms. If intolerant with nausea give vaginally. 1.25mg qhs 1 wk, then BID.
- Causative drugs should be withdrawn if possible and hypothyroidism treated.
- Ergot-derived dopamine agonists (**bromocriptine and cabergoline**) can bind to 5-HT2B receptors in the heart and elsewhere and have been associated with fibrotic reactions, particularly tricuspid valve regurgitation, when used in high doses in patients with Parkinson's disease. Systematic screening for cardiac fibrosis is unnecessary in low doses, but if dopamine agonist therapy is prolonged, **periodic screening by echocardiography** or use of non-ergot agents (quinagolide) may be indicated.
- There's limited data on safety in pregnancy for Cabergoline and Quinagolide. **Bromocriptine** is the longest-established therapy and therefore **preferred if pregnancy** is planned
- **The only pituitary tumor that is firstly treated medically**
- Always medical in case of pregnancy never surgical

2 Surgery and radiation

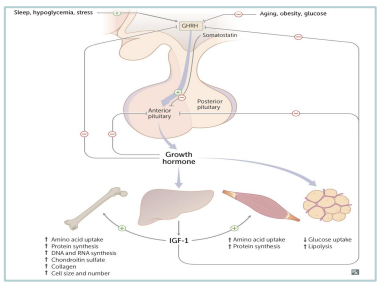
- If the tumor is causing pressure symptoms or if medical therapy failed
- Surgical removal of the tumour via a transsphenoidal approach*, combined with post-operative radiotherapy for large tumours, often restores normoprolactinaemia but there is a high rate of late recurrence (50% at 5 years)

*Access to the pituitary is achieved through the nasal cavity, sphenoid sinus and sphenoid bone.

2- Growth hormone deficiency

◀ Growth hormone

- A polypeptide hormone that is released from the somatotrophs of anterior pituitary
- Action is mediated by **IGF-I** which is produced by the liver
- Half life is 20-50 mins and has a binding protein (GHBPs)
- **Pulsatile secretion**: variable level in the blood
- Binds to its receptor on cell- surface: cytokine receptor
- Lack intrinsic enzyme activity
- **GHRH stimulates it, somatostatin inhibits.**
- Has similar receptor structure to others: leptin, IL-2, PRL
- Controlled by Hypothalamic pituitary axis and peripheral factors.



◀ Growth hormone Changes ★

	Increase	Decrease
Physiology	sleep[1,2], exercise[3], stress, fasting (hypoglycemia), Puberty.	↑glucose, ↑ FFAs.
Pathologic	Liver cirrhosis, AN, Chronic renal failure, starvation	↑ or ↓in T4, Obesity
Pharmacologic	• Estrogen, ACTH, ADH, GHRH, Ghrelin. • dopamine agonist. • K infusion, serotonin arginine and Insulin.	Somatostatin, GH,GC, PG

◀ Growth hormone deficiency

Clinical Features	**In Children:** will present with **short stature**[4] (pituitary dwarfism)	**In Adults:** will lead to metabolic syndrome (dyslipidemia, hypertension, risk of CVD, truncal obesity, reduced bone density and increase tendency for bone fractures) so it is important for its complications
Investigations	• GH, IGF-I level (screening[5]). • **Dynamic testing:** clonidine[6] stimulation test, glucagon stimulation, exercise testing, arginine-GHR, insulin tolerance testing. • **MRI** pituitary to rule out pituitary adenoma. • In pediatric **X-ray of hands:** delayed bone age (Diagnostic)	
Management	Growth Hormone replacement therapy (only given for pediatrics & after excluding other causes of GH deficiency such as adenoma. adults are usually not given replacement therapy unless they have low bone density (osteoporosis), central obesity or socially withdrawn.	

1- This is thought to be the reason why infants sleep for many hours (to grow).
2- So when taking a blood sample of a sleeping patient, GH levels should be high. If it's found to be low during sleep → GH deficiency.
3- Measuring GH level after a physical exercise should show high levels of GH.
4- The commonest cause for short stature is familial "genetics", not growth hormone deficiency.
5- when screening the hormones, always go for IGF-1 because its levels are constant, while GF has diurnal rhythm, thus not reliable, also, why do we need stimulation tests after screening IGF-1? Because IGF-1 is affected by nutrition (malnourished people and uncontrolled diabetes lead to low IGF-1)
6- Anti-Hypertensive drug with growth hormone stimulating properties.

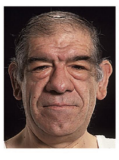
3- Growth hormone excess (Acromegaly/Gigantism)

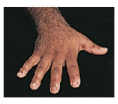
◀ Introduction

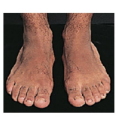
- Excessive GH production leads to **gigantism in children** (if occured **before fusion** of the epiphyses of the long bones) which will lead to high linear growth and **acromegaly in adults**.
- **98% of cases are due to GH pituitary adenoma**[1]
- ⅓ of all functional adenomas are GH adenomas.
- Stimulates growth of skin, connective tissue, cartilage, bone, and viscera.
- Induce **Nitrogen retention**, insulin antagonism, and lipogenesis.
- Can be caused by **Exogenous abuse of Growth hormone.**

◀ Clinical features[2] ★

- Old photographs of the patient may be useful to demonstrate a change in appearance and physical features. The onset is insidious with many years between onset of symptoms and diagnosis. (See **pic A**)
- The most common complaints are **headache** and **sweating**. (bad body odor due to the excessive sweating)
- **irreversible cardiovascular effect: (major cause of death)**
  - **Cardiomegaly and CHF with Diastolic dysfunction being an early sign of cardiomyopathy.**
  - **HTN** in 40%, LVH in 50% and they present with **Obstructive sleep apnea** (due to Neck enlargement)
- **Impaired glucose tolerance → Diabetes Type 2**
- **Carpal tunnel syndrome (Median nerve compression due to the overgrowth of soft tissues)**
- Hypertension(Due to CVS complications + enlarged kidney)
- There's an increased risk of tumors such as leiomyomata and colon polyps
- **Acral enlargement**[3]**:** large thick hands & feet with **osteoarthritis**
- **gross features of acromegaly: Face gross features, enlarged tongue,lower jaw overgrowth (overbite) and spacing of the teeth**
- Galactorrhea (Due to co-secretion of prolactin from the tumor)
- Gingiva enlargement, constipation and **deep voice**
- May have mass effect → Bitemporal hemianopia (mechanical pressure → visual field defect), hypopituitarism
- **Reduced overall survival by an average of 10 years**

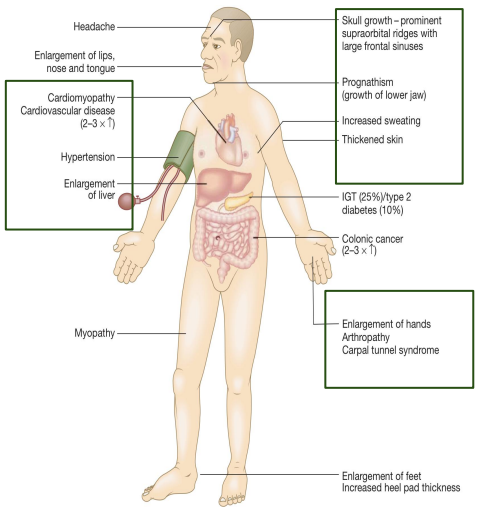


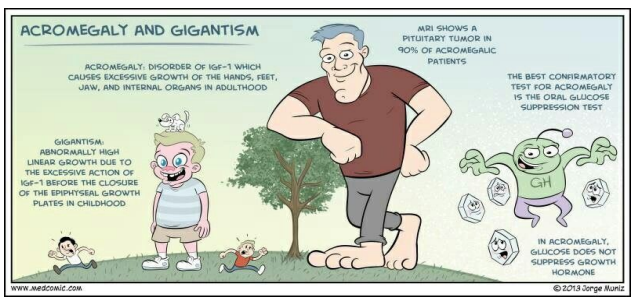




Signs

Prominent supraorbital ridge
Prognathism
Interdental separation
Large tongue
Hirsutism
Thick greasy skin
Spade-like hands and feet
Tight rings
Carpal tunnel syndrome
Visual field defects
Galactorrhoea
Hypertension
Oedema
Heart failure
Arthropathy
Proximal myopathy
Glycosuria
(plus possible signs of hypopituitarism)





1- other very rare ectopic causes include Carcinoid tumors which will lead to the release of GHrH ultimately leading to acromegaly
2-around 40% of acromegalic patients are diagnosed by internists, ophthalmologists if they have visual disturbances, dentists due to maxillary teeth separation, mandibular prognathism, and overbite, gynecologists due to menstrual irregularities and infertility, rheumatologists if they suffer from joint problems, or pulmonologist if they have obstructive sleep apnea
3- Acral, referring to the peripheral parts of the body, includes arms and hands, legs and feet, and nails, plus the ears and nose.

3- Growth hormone excess *cont.*

(Acromegaly/Gigantism)

◀ Investigations

- **Biochemical (hormonal):**
  - **Initial test (screen): Measure IGF-1 (insulin like growth factor-1).** (Will be high in acromegaly)
  - **Confirmatory Test: 75g OGTT (oral glucose tolerance test)for GH suppression**; serum GH should be measured 2 hours after an oral glucose load, in normal subjects, plasma GH suppresses to below 0.5 µg/L (approximately 2 mIU/L). In acromegaly, GH does not suppress and in about 30% of patients there is a paradoxical rise.
  - **Random GH** level is not useful due to the wide physiologic fluctuation of GH levels
  - **Fasting and random blood sugar**, HbA1c, Lipid profile
  - **Pituitary Function** (LH,FSH.**PRL**, TSH, ACTH, cortisol, testosterone, T4).
- **Anatomical (Imaging):**
  - **MRI** or CT for the pituitary
  - **Echo:** Diastolic dysfunction as an early sign of cardiomyopathy
  - **X-ray:** thick heel pad ≥22mm
  - **Colonoscopy:** Screening for colonic neoplasms, there is an increase in deaths due to neoplasia, particularly **large bowel tumours**; guidance advocates regular colonoscopy to detect and remove colonic polyps in order to reduce the risk of colonic cancer is indicated.

Dr: whats the most reliable screening test? IGF-1 NOT GH

◀ Treatment

Goal: Lower the serum insulin-like growth factor to normal for age/gender.

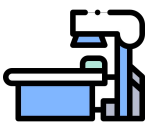
1 Surgery (1st line)

- **Transsphenoidal surgical resection is the treatment of choice.**
- **Complications:** hypopituitarism, diabetes insipidus, CSF rhinorrhoea and infection.
- Note: In case of macroadenomas, its very hard to remove the whole tumor due to its extension to critical areas like cavernous sinuses which can lead to hemorrhage in case of the rapture of internal carotid artery so we do a debulking surgery (reduction of as much bulk of the tumor without complete eradication) (incomplete surgical excision)

2 Medical (2nd line)

- Normally used when **surgery alone has failed** to reduce GH and IGF-I levels to normal.
  - **Somatostatin analogues (octreotide, lanreotide or pasireotide).**
  - Dopamine agonist (**bromocriptine or cabergoline**) "especially **if associated with prolactin excess**"
  - **Didn't work?** use GH receptor antagonist (Pegvisomant)

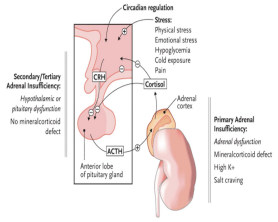
3 Radiotherapy (3rd line)

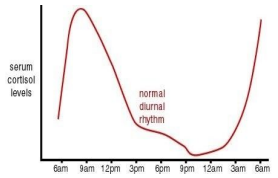


- Used if surgical excision is incomplete and in combination with medical treatment as the response is slow (10 years or more).
- **Complications:** hypopituitarism

4- Cushing disease

◀ Introduction ★





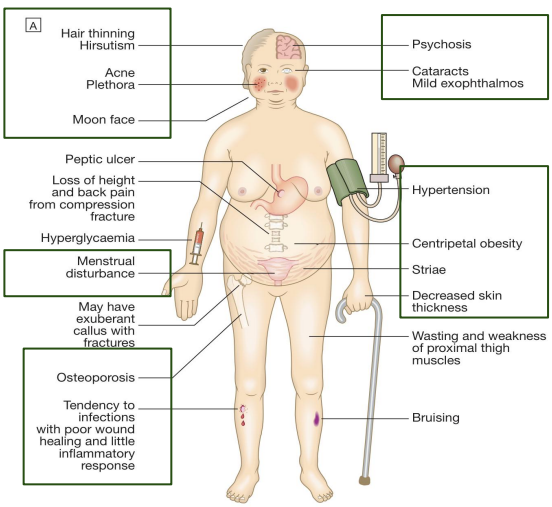
- Cortisol is released from the adrenal cortex
- Commonest cause of Cushing Syndrome is Exogenous **(iatrogenic)**: Prolonged glucocorticoid therapy → hypercortisolism → decreased ACTH → bilateral adrenal atrophy. Abrupt steroid stoppage is prohibited.
- Cortisol and ACTH normally have a stable circadian rhythm (8-9am) which can be altered by: **Physical stress, Psychological stress, CNS and pituitary disorder, liver and renal failure.** has the highest level at 5am (+500).
- In Cushing's Disease there's an abnormally high level of ACTH.
- Cushing's Disease is more common in females by 3-8 times than in males, yet it's still not that common (5-25 per million).
- Cushing's disease must be distinguished from Cushing's syndrome. The latter is a general term which refers to the abnormalities resulting from a chronic excess of glucocorticoids whatever the cause, whereas Cushing's disease refers to excess glucocorticoids resulting from inappropriate ACTH secretion from the pituitary.
- If the ACTH is low and Cortisol is high, then the problem is from the adrenal cortex
- If the ACTH is High and Cortisol is high, then the problem is from the Pituitary.

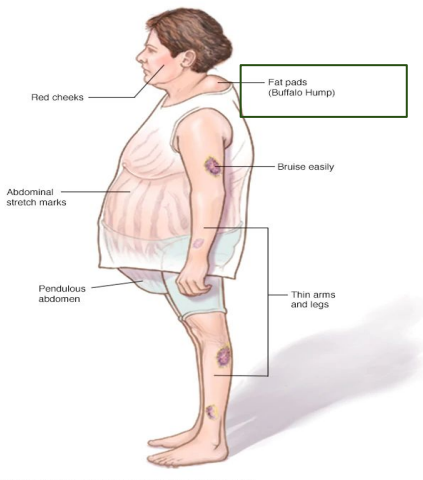
◀ Clinical features

- **Moonface with buffalo hump (dorsocervical fat pads) (we dont use the term buffalo hump because its insulting to the patient), purple striae (wide >1cm) and supraclavicular fat pad**
- **Glucose intolerance (60%)** (cortisol has anti-insulin effect)
- **Central obesity** characterized by thin limbs and striae
- **Hirsutism**[1] (Only in cushing's **disease**) and virilization
- **Osteoporosis** with cutaneous fungal infection and vertebral fractures → admitting to OR (50%), 20% with fractures
- **Hypertension (80%) with hypokalemia**
- **proximal muscle weakness & thin extremities** (complain of difficulty when performing prayers and climbing stairs)
- **ECG**: high QRS voltage, inverted T-wave
- **Diastolic dysfunction, interventricular septal hypertrophy, LVH**
- Depression with other psychological disorders and oligo or amenorrhea
- OSA (33% mild, 18% severe), Needs respiratory assessment and careful use of sedative during surgery.
- Thin skin → difficult IV cannulation, poor wound healing, visible blood vessels
- Glaucoma with Acne[1], easy bruising, depression, ecchymosis, and infertility

Signs

Moon face	Kyphosis
Plethora	'Buffalo hump' (dorsal fat pad)
Depression/ psychosis	Central obesity
Acne	**Striae (purple or red)**
Hirsutism	Rib fractures
Frontal balding (female)	Oedema
Thin skin	**Proximal myopathy**
Bruising	Proximal muscle wasting
Poor wound healing	Glycosuria
Pigmentation	
Skin infections	
Hypertension	
Osteoporosis	
Pathological fractures (especially vertebrae and ribs)	





1. Due to the adrenal androgens (DHA, DHAS, Androstenedione).

4- Cushing disease *cont.*

◀ Investigations

- **Biochemical (hormonal):**
  - **Best initial: 24- hour urinary free cortisol measurements:** It is simple but less reliable. However,repeatedly normal values render the diagnosis unlikely, but some people with Cushing's syndrome have normal values on some collections (approximately 10%).
  - **2nd: Overnight 1mg dexamethasone (low dose) suppression testing (outpatient screening test):** is slightly simpler, but has a higher false-positive rate.
  - **3rd: ACTH circadian rhythm:** Show loss of the normal circadian fall of plasma cortisol at 24:00 h in patients with Cushing's syndrome (normal rhythm change in people with night shifts).
  - **48-hour low-dose dexamethasone test (Most sensitive, >97%):** Normal individuals suppress plasma cortisol to **less than 50nmol/L.** People with Cushing's syndrome fail to show complete suppression of plasma cortisol levels (although levels may fall substantially in a few cases)
  - **Midnight salivary cortisol:** Can be collected at home for the diagnosis and surveillance of Cushing's, removing the need for a hospital stay.
- **Anatomical (Imaging):**
  - **MRI** pituitary for pituitary adenoma. In Cushing's disease, the pituitary tumour is usually a microadenoma (< 10 mm in diameter); hence other features of a pituitary macroadenoma (hypopituitarism, visual failure or disconnection hyperprolactinaemia) are rare.

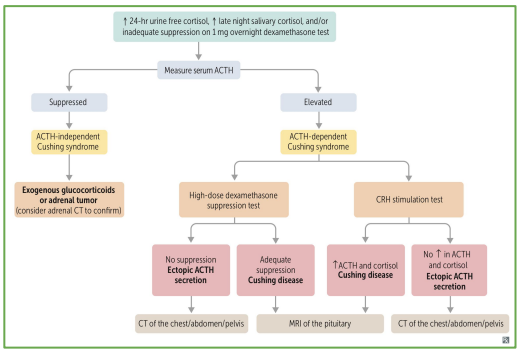


Table 19.11 Dexamethasone suppression test in the diagnosis of Cushing's syndrome

Test and protocol	Measure	Normal test result or positive suppression	Use and explanation
Dexamethasone (for Cushing's)			
Overnight			
Take 1 mg on going to bed at 23:00 hours	Plasma cortisol at 09:00 hours next morning	Plasma cortisol <100 nmol/L	Outpatient screening test Some 'false positives'
'Low-dose'			
0.5 mg 6-hourly Eight doses from 09:00 hours on day 0	Plasma cortisol at 09:00 hours on days 0 and +2	Plasma cortisol <50 nmol/L on second sample	For diagnosis of Cushing's syndrome
'High-dose' used in differential diagnosis			
2 mg 6-hourly Eight doses from 09:00 hours on day 0	Plasma cortisol at 09:00 hours on days 0 and +2	Plasma cortisol on day +2 less than 50% of that on day 0 suggests pituitary-dependent disease	Differential diagnosis of Cushing's syndrome Pituitary-dependent disease suppresses in about 90% of cases

Plasma cortisol values are very dependent upon the assay used – local reference ranges must be consulted.

High-dose (2mg) dexamethasone suppression test is used to differentiate between pituitary based and ectopic based ACTH cushing's. Test failure of significant plasma cortisol suppression suggests an ectopic source of ACTH(eg:Lung SCC) or an adrenal tumour.

◀ Treatment

- **First line:** Transsphenoidal surgery[1] (**treatment of choice**)
- **Second line:** Pituitary irradiation[1] (if entire adenoma couldn't be resected)
- **Last resort:** Laparoscopic bilateral adrenalectomy may cause Nelson's syndrome[2] which is characterized by increased pigmentation due to high levels of ACTH.

Treatment for pregnant women
- **1st Trimester:** Surgery
- **2nd Trimester:** Adrenal Enzyme Inhibitors or surgery
- **3rd Trimester:** Early delivery, enzyme inhibitors until lung maturity.

◀ Prognosis

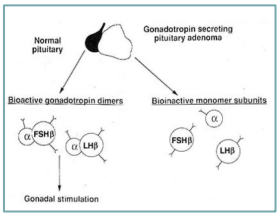
- Untreated Cushing's syndrome has a very poor prognosis, with death from **venous thromboembolism**, **hypertension**, **myocardial infarction**, **infection** and **heart failure**.

1- Cortisol hypersecretion should be controlled prior to surgery or radiotherapy using metyrapone,ketoconazole, or etomidate infusion.
2- Enlargement of intrasellar pre-existing ACTH–secreting pituitary adenoma after bilateral adrenalectomy for refractory Cushing disease → high ACTH (hyperpigmentation), mass effect (headaches, bitemporal hemianopia). Treatment: transsphenoidal resection, postoperative pituitary irradiation for residual tumor.

Other etiologies

01 Gonadotrophic adenoma: "Skipped by male's doctor"

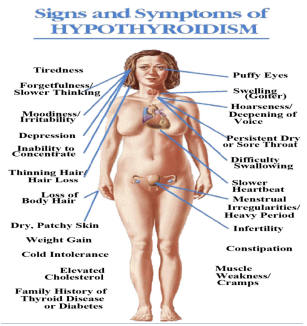
- Usually considered **non-functioning adenoma** (Secrete inefficiently and variably).
- Present with **neurological symptoms** (vision most commonly).
- Very rare and difficult to diagnose:
  - Rule out other adenomas
  - Prepubertal girls → Breast development, vaginal bleeding
  - Premenopausal → olig, Amenorrhea
- **Hormonal findings:**
  - High FSH and low LH, which is often accompanied by hypersecretion of FSH **alpha-subunit** (see the fig)
  - Less often by hypersecretion of LH.
  - High estradiol, FSH, thickened endometrium and polycystic ovaries
- **Treat it by:** Trans-sphenoidal surgery if large with or without radiation



Note: (How to know whether high FSH is a result of menopause or gonadotrophic adenoma in women? in gonadotroph adenoma there will be in addition to high FSH, high estradiol, thickened endometrium and\or polycystic ovaries)

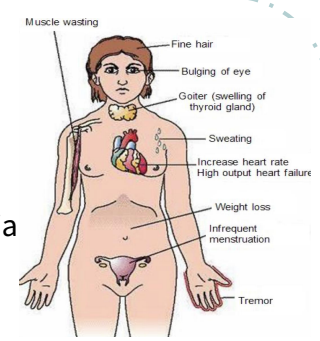
02 Central hypothyroidism:

- Low TSH, Low free T4 and T3
- **S&S:**
  - Fatigue, weight gain, irregular menses, dry skin, depression, cold intolerance, increase sleep, slow thinking
  - Obesity, Depressed face, eyebrow, hair loss, constipation.
- **Diagnosis:**
  - **Biochemical:** Low T4 and Low TSH
  - **Anatomical:** MRI
- **Treatment:**
  - Thyroxine replacement
  - Surgical removal of pituitary adenoma if large



03 Hyperthyroidism:

- Very rare < 2.8 %
- **S&S:**
  - Goitre, palpitations, twitching or trembling, warm skin and excessive sweating, red palms of your hands, loose nails, urticaria
  - patchy hair loss or thinning , diarrhea.
  - weight loss – often despite an increased appetite.
- **Diagnosis:**
  - **Biochemical:** High TSH, FT4, FT3
  - **Anatomical:** MRI
- **Treatment:**
  - Medical therapy: Somatostatin Analogue
  - Surgical resection of adenoma (first line)



2 and 3 will be discussed in details in a separate lecture

Other etiologies *cont.*

04 Hypopituitarism[1]:

- There is generally a progressive loss of anterior pituitary function. **GH and gonadotropins are usually firstly affected**. **Hyperprolactinaemia**, rather than prolactin deficiency, occurs relatively early because of loss of tonic inhibitory control by dopamine. **TSH and ACTH are usually last to be affected.**
- **76% caused by a tumor or treatment of tumor**
  - Mass effect of adenoma on other hormones.
  - Surgical resection of non-adenomatous tissue or Radiation of pituitary (Hormones have to be checked 6 Months after then yearly).

Box 21.10 Causes of hypopituitarism

Congenital
- Isolated deficiency of pituitary hormones (e.g. Kallmann's syndrome)
- *PDU1F1 (Pit-1), Prop1, HESX1* mutations

Infective
- Basal meningitis (e.g. tuberculosis)
- Encephalitis
- Syphilis

Vascular
- Pituitary apoplexy
- Sheehan's syndrome (postpartum necrosis)
- Carotid artery aneurysm

Immunological
- Autoimmune (lymphocytic) hypophysitis
- Pituitary antibodies

Neoplastic
- Pituitary or hypothalamic tumour
- Craniopharyngioma
- Meningioma
- Gliomas
- Pinealoma
- Secondary deposits, especially breast
- Lymphoma

Traumatic
- Skull fracture through base
- Surgery, especially transfrontal
- Perinatal trauma

Infiltrations
- Sarcoidosis
- Langerhans' cell histiocytosis
- Hereditary haemochromatosis
- Hypophysitis:
  - Postpartum
  - Giant cell

Others
- Radiation damage
- Fibrosis
- Chemotherapy
- Immunotherapy (ipilimumab, pembrolizumab, nivolumab)
- Empty sella syndrome

'Functional'
- Anorexia nervosa
- Starvation
- Emotional deprivation

- **13% caused by extra-pituitary tumors eg: craniopharyngioma[2]** (most common childhood tumor that causes hypopituitarism),**8% unknown** , **1% sarcoidosis, 0.5% Sheehan's syndrome** (caused by excess blood loss (hemorrhage) or extremely low blood pressure during or after labor leading to infarction of pituitary gland)
- **Sheehan syndrome:** ischemic infarct of pituitary following postpartum bleeding; pregnancy-induced pituitary growth → Increase susceptibility to hypoperfusion. Usually presents with failure to lactate, absent menstruation, cold intolerance
- **Clinical features of hypopituitarism:**
  - Symptoms of secondary hypothyroidism and adrenal failure
  - Gonadotrophin and thus gonadal deficiencies, Hyperprolactinaemia
  - GH deficiency, Weight may increase
  - Classic picture of pallor with **hairlessness ('alabaster skin').**
- **Treatment:** hormone replacement therapy (CS, thyroxine[3], sex steroids, GH) **(See table)**

Table 19.8 Replacement therapy for hypopituitarism

Axis	Usual replacement therapies
Adrenal	Hydrocortisone 15–40 mg daily (starting dose 10 mg on rising/5 mg lunchtime/5 mg evening) (Normally no need for mineralocorticoid replacement)
Thyroid	Levothyroxine 100–150 µg daily
Gonadal	
Male	Testosterone intramuscularly, orally, transdermally or implant
Female	Cyclical oestrogen/progestogen orally or as patch
Fertility	HCG plus FSH (purified or recombinant) or pulsatile GnRH to produce testicular development, spermatogenesis or ovulation
Growth	Recombinant human GH used routinely to achieve normal growth in children Also advocated for replacement therapy in adults where GH has effects on muscle mass and wellbeing
Thirst	Desmopressin 10–20 µg one to three times daily by nasal spray or orally 100–200 µg three times daily Carbamazepine, thiazides and chlorpropamide are very occasionally used in mild diabetes insipidus
Breast (prolactin inhibition)	Dopamine agonist (e.g. cabergoline, 500 µg weekly)

05 Cortisol low (hypoadrenalism):

- Could be primary adrenal insufficiency (caused by TB, malignancy, etc.) or secondary/central adrenal insufficiency (adenoma)
- **S&S:** Nausea, Vomiting, abdominal pain, Diarrhea Dizziness and weakness, Tiredness, Muscle ache, hypotension, weight loss.
- Investigation: measure ACTH, cortisol, dynamic testing (short synacthen)
- **Management:** Cortisol replacement, surgical removal of adenoma if central.

06 Infiltrative Lesions:

Hereditary Hemochromatosis

- Caused by Iron deposition in pituitary (haemochromatosis) or Gonadotropin deficiency(most common)
- **Treatment:** repeat phlebotomy.

Pituitary Apoplexy

- Sudden hemorrhage seen on MRI into pituitary **"urgent condition"** with severe, severe sudden headache, diplopia, hypopituitarism with sudden ACTH def (Is life-threatening hypotension)
- **Treatment:** surgical decompression.

1-Panhypopituitarism refers to deficiency of all anterior pituitary hormones; it is most commonly caused by pituitary tumours, surgery or radiotherapy. Vasopressin (ADH) will only be significantly affected if the hypothalamus is involved by a hypothalamic tumour or major suprasellar extension of a pituitary lesion, or if there is an infiltrative/inflammatory process. Posterior pituitary deficiency with diabetes insipidus is rare in an uncomplicated pituitary adenoma.
2-benign non-functioning childhood tumours that develop in cell rests of Rathke's pouch, and may be located within the sella turcica, **commonly in the suprasellar space**. clinical features include hyperphagia and obesity, loss of the sensation of thirst and disturbance of temperature regulation.
3- **Thyroid replacement should not commence until normal glucocorticoid function** has been demonstrated or replacement steroid therapy initiated, as an adrenal 'crisis' may otherwise be precipitated.

Posterior Pituitary Disorders

◀ Diabetes Insipidus

Types[1]

- **Central DI:** Deficiency of vasopressin (ADH), caused by a hypothalamic disorder (adenoma of pituitary does not cause it because it is only stored there)
- **Nephrogenic DI:** Renal resistance to ADH action
- **Psychogenic DI:** is an excessive water intake seen in some patients with mental illnesses such as schizophrenia.

Causes[2]

Central DI:

- Abrupt onset, 30-50% are idiopathic (Dec. production by hypothalamus).
- Neurosurgery or head trauma
- Primary or secondary tumours.
- Infiltrative disease (sarcoidosis, histiocytosis).
- Vascular disease e.g. Stroke, hypoxia
- iatrogenic: cut of the stalk during surgery
- Rare with sheehan's (Mild, undetectable)

Nephrogenic DI:

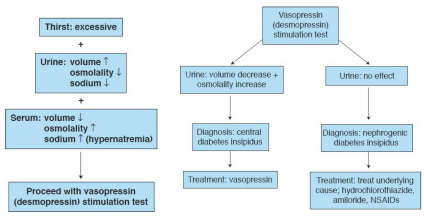
- ↓K or↑Ca.
- Lithium.
- Renal tubular acidosis.
- Sickle cell disease.
- Familial mutation in ADH receptor.
- Chronic pyelonephritis
- Amyloidosis
- Myeloma

Symptoms

Abrupt onset of **polyuria** (1st manifestation), **polydipsia** (2nd manifestation) and **thirst**

Investigations

- **Urine:** ↑**urine volume** (2 – 15 L/day), ↓**urine osmolality,** ↓specific gravity .
- **Serum Na+:** usually **high** (Because ADH cause fractional excretion of Na in urine so lack of ADH result in high serum Na) ⟶ Neurological symptoms.
- High or high-normal plasma osmolality (in primary polydipsia, plasma osmolality tends to be low).



Water deprivation test (To differentiate between CDI, NDI and PDI)

- Restrict P.O(oral) fluids or administer hypertonic saline to increase serum osmolality to 295-300 mosmol/kg (normal: 275-290).
- **Central DI:** urine osmolality will still low (Before giving vasopressin) and returns to normal after administer vasopressin.
- **Nephrogenic DI:** exogenous vasopressin does not alter urine osmolality much.
- **Psychogenic DI:** Urine will be become concentrated as they aren't really a problem with either the pituitary nor the kidney.

Treatment

Central DI:

DDAVP (Desmopressin Acetate)

- Synthetic analog of ADH
- Not catabolized by vasopressinase ⟶No vasopressor action
- Administered intranasally or orally
- Titrate 10-20ug qd or bid
- Safe in pregnancy and breastfeeding.

Nephrogenic:

- Correct underlying cause.
- Hydrochlorothiazide[3] used to sensitize the renal tubules to endogenous vasopressin.

Primary Polydipsia:

- Psychiatric management.

1- Patients with Central DI and Nephrogenic DI can't fast Ramadan (they lose so much fluids without it being replaced due to fasting).

2- DIDMOAD (Wolfram's) syndrome is a rare autosomal recessive disorder comprising diabetes insipidus, diabetes mellitus, optic atrophy and deafness, and is caused by mutations in the WFS1 gene on chromosome 4. MRI may show an absent or poorly developed posterior pituitary.

3- in addition to carbamazepine (200–400 mg daily) and chlorpropamide (200–350 mg daily) but these are rarely used.

Posterior Pituitary Disorders *cont.*

Syndrome of inappropriate antidiuretic hormone secretion(SIADH)

- Inappropriate secretion of **ADH** (also called vasopressin) leads to retention of water and hyponatraemia.

Clinical Features	• **The presentation is usually vague**, with confusion, nausea, irritability and, later, fits and coma. There is no oedema. **Mild symptoms usually occur with plasma sodium levels below 125 mmol/L and serious manifestations are likely below 115 mmol/L.** The elderly may show symptoms with mild abnormalities. • This syndrome must be distinguished from **dilutional hyponatremia** due to excess infusion of glucose/water solutions or diuretic administration
Investigations	• **Dilutional hyponatremia (most common)** due to excessive water retention euvolemia (in contrast to hypovolaemia of sodium and water depletion states) • **Low plasma osmolality with 'inappropriate' urine osmolality >100** mOsm/kg (and typically higher than plasma osmolality) • **Continued urinary sodium excretion >30 mmol L** (lower levels suggest sodium depletion or 'hypovolaemic hyponatraemia', and should respond to 0.9% saline infusion) • **Absence of hypokalemia (or hypotension)** • **Normal renal and adrenal and thyroid function.** • **ACTH deficiency can give a very similar biochemical picture to SIADH**; therefore it is necessary to ensure that the hypothalamic–pituitary–adrenal axis is intact, **particularly in neurosurgical patients**, in whom ACTH deficiency may be relatively common.
Treatment	• **The underlying cause should be corrected where possible.** **Symptomatic relief can be obtained by the following measures:** • **Fluid intake** should be restricted to **500–1000 mL daily**. If tolerated and complied with, this will correct the biochemical abnormalities in almost every case. • **Demeclocycline** (600–1200 mg daily) is given if water restriction is poorly tolerated or ineffective; **this inhibits the action of vasopressin on the kidney**, causing a reversible form of nephrogenic diabetes insipidus. However, it often causes photosensitive rashes. • **Hypertonic saline** may be indicated when the syndrome is very severe (i.e. acute and symptomatic), but this is potentially dangerous and should only be used with extreme caution. • **Vasopressin V2 antagonists**, e.g. tolvaptan 15 mg daily, are being used with good results.

Causes of SIADH →

? Box 21.54 Common causes of the syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Tumours
- Small-cell carcinoma of lung
- Prostate
- Thymus
- Pancreas
- Lymphomas

Pulmonary lesions
- Pneumonia
- Tuberculosis
- Lung abscess

Central nervous system causes
- Meningitis
- Tumours
- Head injury
- Subdural haematoma
- Cerebral abscess
- Systemic lupus erythematosus
- Vasculitis

Metabolic causes
- Alcohol withdrawal
- Porphyria

Drugs
- Chlorpropamide
- Carbamazepine
- Cyclophosphamide
- Vincristine
- Phenothiazines

Summary

	Anterior Pituitary Disorders	Hypothalamus & Posterior Pituitary Disorders
Hypersecretion	**1- Prolactinoma:** • High prolactin level . • Presents with galactorrhea, decrease lipido and amenorrhea. • Tx: Medically (Bromocriptine). **2- GH Secreting Adenoma:** • High IGF-1. • Causes acromegaly (in adults), gigantism (in children). • Presents with DM, facial changes, CVD and Acral enlargement. • Tx: Surgery (1st line)	**Syndrome Of Inappropriate Antidiuretic Hormone (SIADH):** • Caused by disordered hypothalamic–pituitary secretion or ectopic production of ADH. • Causes low serum Na and osmolality, also high urine Na and osmolality. • Tx: Treating the underlying • cause and fluid restriction.
	3- ACTH secreting adenoma: • Result in Cushing DISEASE. • High cortisol, high ACH. • Presents with typical cushing features. • Tx: Surgery followed by radiation.	**4- Gonadotropin secreting adenomas:** • Hypersecretion of **FSH**, which is often accompanied by hypersecretion of FSH **alpha-subunit** • Present with **neurological symptoms**
Hyposecretion	Deficiency of hypothalamic-releasing hormones or pituitary hormones Causes: (**Seven I's**) • **Invasive: pituitary tumors.** • **Infarction: Sheehan's syndrome.** • **Iatrogenic: surgery.** • **Infiltration: Sarcoidosis, hemochromatosis.** • **Injury: trauma.** • **Infections: TB.** • **Idiopathic.** Tx: remove the cause and start HRT.	**Diabetes insipidus:** • Decreased the amount of ADH. • Manifest polydipsia and polyuria. • Serum Na is high, ↑ urine volume, and ↓ urine osmolality. Tx: medically (Desmopressin Acetate) Synthetic analog of ADH if the cause centrally due to pituitary source.

Summary of treatment

i 18.57 Therapeutic modalities for functioning and non-functioning hypothalamic and pituitary tumours

	Surgery	Radiotherapy	Medical	Comment
Non-functioning pituitary macroadenoma	1st line	2nd line	–	
Prolactinoma	2nd line	2nd line	1st line Dopamine agonists	Dopamine agonists usually cause macroadenomas to shrink
Acromegaly	1st line	2nd line	2nd line Somatostatin analogues Dopamine agonists GH receptor antagonists	Medical therapy does not reliably cause macroadenomas to shrink Radiotherapy and medical therapy are used in combination for inoperable tumours
Cushing's disease	1st line	2nd line	2nd line Steroidogenesis inhibitors Pasireotide	Radiotherapy may take many years to reduce ACTH excess and medical therapies may be used as a bridge. Bilateral adrenalectomy may also be considered if the pituitary tumour is not completely resectable
Craniopharyngioma	1st line	2nd line	–	

(ACTH = adrenocorticotrophic hormone; GH = growth hormone)

Assessment of Pituitary Function:

- **Baseline:** TSH, FT4(T4), LH+FSH with Testosterone or Estradiol, Prolactin, GH, IGF-I ACTH, cortisol and electrolyte.
- **MRI** of the brain + **Neuro-ophthalmic for evaluation of visual field**.
- **Cardiac and respiratory assessment** with **ENT** for Endonasal evaluation for surgical approach.
- **Anesthesiologist** for airway and perioperative monitoring
- **Neurosurgeon**
- **Preop hormonal replacement:** maybe need to be covered with stress dose of HC

Summary from Kumar

Table 19.4 Characteristics of common pituitary and related tumours

Tumour or condition	Usual size	Most common clinical presentation
Prolactinoma	Most <10 mm (microprolactinoma)	Galactorrhoea, amenorrhoea, hypogonadism, erectile dysfunction
	Some >10 mm (macroprolactinoma)	As above plus headaches, visual field defects and hypopituitarism
Acromegaly	Few mm to several cm	Change in appearance, visual field defects and hypopituitarism
Cushing's disease	Most small: few mm (some cases are hyperplasia)	Central obesity, cushingoid appearance (local symptoms rare)
Nelson's syndrome	Often large: >10 mm	Post-adrenalectomy, pigmentation, sometimes local symptoms
Non-functioning tumours	Usually large: >10 mm	Visual field defects; hypopituitarism (microadenomas may be incidental finding)
Craniopharyngioma	Often very large and cystic (skull X-ray abnormal in >50%; calcification common)	Headaches, visual field defects, growth failure (50% occur below age 20; about 15% arise from within sella)

Table 19.5 Comparisons of primary treatments for pituitary tumours

Treatment method	Advantages	Disadvantages
Surgical		
Trans-sphenoidal adenomectomy or hypophysectomy	Relatively minor procedure Potentially curative for microadenomas and smaller macroadenomas	Some extrasellar extensions may not be accessible Risk of CSF leakage and meningitis
Transcranial (usually transfrontal)	Good access to suprasellar region	Major procedure; danger of frontal lobe damage High chance of subsequent hypopituitarism
Radiotherapy		
External (40–50 Gy)	Non–invasive Reduces recurrence rate after surgery	Slow action, often over many years Not always effective Possible late risk of tumour induction
Stereotactic	Precise administration of high dose to lesion	Long-term follow-up data limited
Medical		
Dopamine agonist therapy (e.g. bromocriptine, cabergoline)	Non-invasive; reversible	Usually not curative; significant side-effects in minority Concerns about fibrotic reactions
Somatostatin analogue therapy (octreotide, lanreotide)	Non-invasive; reversible	Usually not curative; gallstones; expensive
Growth hormone receptor antagonist (pegvisomant)	Highly selective	Usually not curative; very expensive

Table 19.7 Tests for hypothalamic-pituitary (HP) function

All hormone levels are measured in plasma unless otherwise stated.

Tests **shown in bold** are those normally measured on a single basal 09:00 hours sample in the initial assessment of pituitary function.

Axis	Basal investigations			
	Pituitary hormone	End-organ product/function	Common dynamic tests	Other tests
Anterior pituitary				
HP-ovarian	**LH** **FSH**	**Oestradiol** Progesterone (day 21 of cycle)		Ovarian ultrasound LHRH test[a]
HP-testicular	**LH** **FSH**	**Testosterone**		Sperm count LHRH test[a]
Growth	GH	**IGF-1** IGF-BP3	Insulin tolerance test Glucagon test	GH response to sleep, exercise or arginine infusion GHRH test[a]
Prolactin	**Prolactin**	**Prolactin**	–	–
HP-thyroid	**TSH**	**Free T_4, T_3**		TRH test[a]
HP-adrenal	ACTH	**Cortisol**	Insulin tolerance test Short ACTH (tetracosactide) stimulation test	Glucagon test CRH test[a] Metyrapone test
Posterior pituitary				
Thirst and osmoregulation		**Plasma/urine osmolality**	Water deprivation test	Hypertonic saline infusion

[a]Releasing hormone tests were a traditional part of pituitary function testing, but have been largely replaced by the advent of more reliable assays for basal hormones. They test only the 'readily releasable pool' of pituitary hormones and normal responses may be seen in hypopituitarism.

Lecture Quiz

Q1: You see a 28-year-old woman has noticed a change in her appearance; most notably her clothes do not fit properly and are especially tight around the waist. Her face appears flushed and more rounded than usual, despite exercising regularly and eating healthily her weight has steadily increased over the last 3 weeks. On visiting her GP, he notices her blood pressure has increased since her last visit and she has bruises on her arm. She is especially worried about a brain tumour. The most appropriate investigation would be:

A- Low-dose dexamethasone test
B- High-dose dexamethasone test
C- Urinary free cortisol measurement
D- Computed tomography (CT) scan

Q2: A 38-year-old woman presents to clinic complaining of changes in her appearance and weight gain. She has recently been through a divorce and attributed her weight gain to this. However, despite going to the gym her clothes are still tight, especially around her waist, her face seems puffy and flushed. The most likely diagnosis is:

A- Hyperthyroidism
B- Cushing's disease
C- Hypothyroidism
D- Acromegaly

Q3: A 42-year-old woman presents with visual disturbances. She reports having double vision which was intermittent initially but has now become much more frequent. In addition, she becomes breathless very easily and experiences palpitations. On examination, raised, painless lesions are observed on the front of her shins and finger clubbing. The most likely diagnosis is:

A- De Quervain's thyroiditis
B- Graves' disease
C- Pheochromocytoma
D- Thyroid storm

Q4: A 37-year-old man presents with symptoms of an acute headache, vomiting, malaise and visual disturbance. A neurological examination reveals a bitemporal superior quadrantanopia. A CT scan shows a hyperdense area within the pituitary gland. The most likely diagnosis is:

A. Kallmann's syndrome
B. Septo-optic dysplasia
C. Pituitary apoplexy
D. Sheehan's syndrome

Q5: A 29-year-old man presents to his GP complaining of being constantly thirsty, tired and visiting the toilet more often than usual during the last 4 days. He has noticed his clothes have become more baggy and he now needs to tighten his belt. His parents both have diabetes requiring insulin therapy. A fasting plasma glucose result is most likely to be:

A- 16.3 mmol/L
B- 6.0 mmol/L
C- 9.0 mmol/L
D- 3.0 mmol/L

Q6: A 19-year-old woman presents with concerns about changes to her facial appearance, in particular her nose and jaw seem quite large, she is also quite sweaty and despite using antiperspirants is finding it difficult to control and is afraid of embarrassment at university. A glucose tolerance test is performed and found to be raised. The most appropriate management would be:

A. Trans-sphenoidal surgery
B. Octreotide
C. Bromocriptine
D. Pituitary radiotherapy

Answers: Q1:C | Q2:D | Q3:B | Q4:C | Q5:C | Q6:A

Answers Explanation File!

GOOD LUCK !

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