Pituitary Disorders

Objectives:

- Understand basic pathophysiology and feedback for pituitary hormones.
- Know the clinical approach for common anterior pituitary gland disorders.
- Anatomy and function of hypothalamus and pituitary.
- Clinical presentation, Investigations (laboratory & radiological), lines of management of:
    I. Anterior pituitary disorders.
    II. Posterior pituitary disorders.

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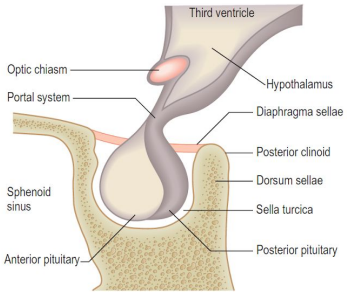
Resources: 435 team + Davidson + kumar + Recall questions step up to medicine.

- Editing file
- Feedback

Basic Review of Hypothalamus & Pituitary Gland

*you can skip Anatomy and embryology of pituitary if you don't have enough time.

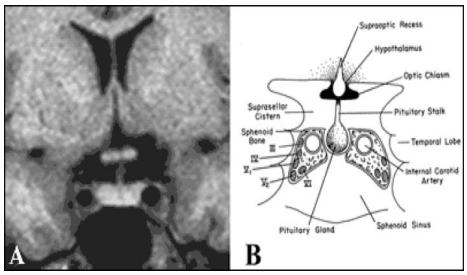
★ Anatomy of Pituitary Gland[1]



- The gland is composed of two lobes, anterior and posterior, and is connected to the hypothalamus by the infundibular stalk below the 3rd ventricle. Infundibular stalk has portal vessels carrying blood from the median eminence of the hypothalamus to the anterior lobe and nerve fibres to the posterior lobe.

Anatomical relations to the pituitary:

- The pituitary gland is enclosed in the sella turcica and bridged over by a fold of dura mater called the diaphragma sellae.
- Inferiorly: Sphenoidal air sinuses.
- Superiorly: diaphragma sellae (Pituitary stalk and its blood vessels pass through the diaphragm)
- Anteriorly: Optic chiasm.
- Laterally: Cavernous sinuses which contain the 3rd, 4th and 6th cranial nerves and the internal carotid arteries (adjacent to temporal lobes).

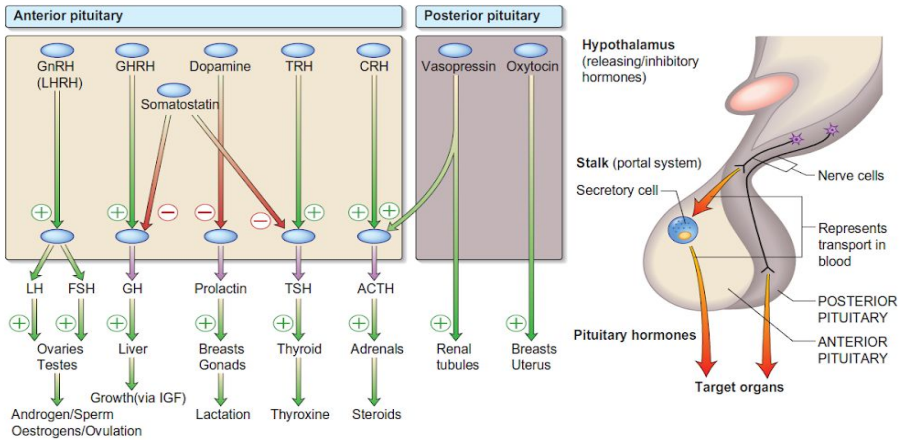


★ Lobes of the pituitary:

Pituitary	Anterior (Adenohypophysis)	Posterior (Neurohypophysis)
Origin	Rathke's pouch (Ectodermal evagination of oropharynx)[2]	Down growth of hypothalamic neural tissue. (as an outpouching from the floor of 3rd ventricle)
	Development of pituitary cells is controlled by a set of transcription growth factors like: Pit-1, Prop-1, Pitx2	
Hormones released	GH , LH, FSH, TSH, ACTH, Prolactin (Go Look For The Adenoma Please)	Oxytocin, ADH
Hormones synthesis	Hormones are Synthesized and Secreted in anterior pituitary.	Synthesized in hypothalamus and stored in posterior pituitary Remember (storage not synthesis)
Arterial supply[3]	Superior hypophyseal	Inferior hypophyseal
Venous drainage	To superior and inferior petrosal sinuses to jugular vein.	
Hypothalamic control	Hormonal signals (releasing and inhibitory hormones)	Neural signals

[1] Anatomy and embryology of the Pituitary is important to Know and understand but **not** for your exam.
[2] Portion of Rathke's pouch → Intermediate lobe. Remnant of Rathke's pouch cell in oral cavity → pharyngeal pituitary. Pituitary remnants can be found in pts with abnormal pituitary embryogenesis.
[3] Superior, middle, and inferior hypophysial arteries (branches of internal carotid artery) running in median eminence from hypothalamus.

	Note: all releasing hormones are stimulatory except dopamine which inhibits prolactin, so pituitary stalk lesion will cause hyperprolactinemia and decrease to all other ant.pit HORMONES	



★ More details about anterior pituitary hormones

*All hypothalamus hormones are stimulatory except Dopamine (decrease the prolactin) and somatostatin (decrease the growth hormone).

Original Cells	Somatotroph	Gonadotroph	Lactotroph	Thyrotroph	Corticotroph
Stimulators	- GHRH - GHS[4]	- GnRH - E2	- TRH - E2[5]	TRH	- CRH - AVP - Gp-130 - Cytokines
Inhibitors	- IGF-1 - Somatostatin (GHIH) - Activin	- Testosterone - E2 - Inhibin	Dopamine	T3, T4 Dopamine Somatostatin GH	Steroid
Hormone	GH (page 15)	LH, FSH	PRL	TSH	ACTH
Target Gland	Liver & other tissues	Ovaries, Testes	Breast & other tissues	Thyroid	Adrenals
Target Hormone	IGF-1	Testosterone, E2		T4	Cortisol
Trophic Effects	- IGF-1 production. - Growth induction. - Insulin antagonism.	**Sex Steroid** - Follicular growth - Germ Cell maturation.	Milk Production. Can inhibit GnRH.	T4 synthesis and secretion	Steroid production. Androgen

[4] GH secretagogues
[5] Estradiol

Pituitary Disorders

★ Classification of diseases of the pituitary

- Function[6]:
  - Hypersecretion: GH, LH, FSH, PRL, TSH, ACTH.
  - Hyposecretion: hypopituitarism (isolated, multiple, pan).
    - Central hypoadrenalism, hypogonadism, hypothyroidism or GH deficiency
    - Panhypopituitarism
- Masses: Any tumour could be either:
  - Non-functioning,
  - Functioning (hypersecretion).
  - With or Without **Mass-effect**[7].

★ Etiology of Pituitary-Hypothalamic lesions

Anterior pituitary	Hypothalamus & posterior pituitary
Non-Functioning tumours: هي نفسها ما تفرز هورمونات لكن ممكن اذا حجمها كبير تضغط عالتراكيب التي حولها فتطلع أعراض حسب الجزء المنضغط Pituitary Adenomas, Pituitary incidentaloma, Craniopharyngioma, Metastatic tumours	
Tumours Causing Hormone <u>Excess (adenomas)</u>: Functioning Pituitary Adenomas[8]: 1. Prolactinoma[9], secreting PRL. 2. Somatotropinoma, GH secreting adenoma: Acromegaly 3. Corticotropinoma, ACTH secreting adenoma: Cushing's disease. 4. Thyrotropinoma (TSH-oma, rare) 5. Other mixed endocrine active adenomas.	**Tumours Causing Hormone <u>Excess</u>:** Syndrome of inappropriate antidiuretic hormone (SIADH)
Tumours Causing <u>inadequate</u> hormone production: hypopituitarism (Isolated, multiple, and pan).	**Tumours causing <u>Inadequate</u> hormone production:** Central diabetes insipidus
• Malignant pituitary tumors: ○ Functional and non-functional pituitary carcinoma. • Metastases in the pituitary: (breast, lung, stomach, kidney). • Pituitary cysts: Rathke's cleft cyst, Mucocoeles, Others. • Empty sella syndrome. • Pituitary abscess, in TB patients. • Lymphocytic hypophysitis, antibodies attacking the pituitary.	

[6] A compressive adenoma in the pituitary will impair hormone production in this order: **G**o **L**ook **F**or **T**he **A**denoma **P**lease

[7] Space occupying lesion (compression symptoms, hypopituitarism)

[8] Know them in this order. according to the most common hormone affected in a FUNCTIONAL adenoma.

[9] Very common. 20-30% of functioning pituitary adenomas.

- Carotid aneurysm.

★ Evaluation of Pituitary Mass

	Functional adenoma	Non-functional adenoma
Epidemiology	- 10% of all pituitary lesions. - Genetic-related: MEN-1, Gs-alpha mutation, PTTG gene, FGF receptor-4.	- 1.5 -31% in autopsy (prevalence). - 10% by MRI most of them <1
C: Clinical	- Function (oversecretion or hyposecretion) - Mass (headache, visual symptoms)	- Asymptomatic, incidentaloma by imaging. - Mass-effect. - Gonadal hypersecretion
B: Biochemical	Screen Test, Confirmatory Test.	▪ GH, LH, FSH, TSH, ACTH: not high. ▪ PRL: low, high, normal.
A: Anatomy	MRI of sella turcica	MRI
Treatment	● Surgical – Medical – Radiation ● Medical – Surgical – Radiation	● Surgery if indicated ● Observation ● Adjunctive therapy: ○ Radiation therapy ○ Dopamine agonist ○ Somatostatin analogue

★ Principles of endocrine investigation

- **Timing of measurement**
  - Release of many hormones is rhythmical (pulsatile, circadian or monthly), so random measurement may be invalid and sequential or dynamic tests may be required.
- **Choice of dynamic biochemical tests**
  - Abnormalities are often characterised by loss of normal regulation of hormone secretion.
  - If hormone deficiency is suspected, choose a stimulation test.
  - If hormone excess is suspected, choose a suppression test.
  - The more tests there are to choose from, the less likely it is that any single test is infallible, so avoid interpreting one result in isolation.
- **Imaging**
  - Secretory cells also take up substrates, which can be labelled.
  - Most endocrine glands have a high prevalence of 'incidentalomas', so do not scan unless the biochemistry confirms endocrine dysfunction or the primary problem is a tumour.
- **Biopsy**
  - Many endocrine tumours are difficult to classify histologically (e.g. adrenal carcinoma and adenoma)

*imaging and biopsy, are more frequently reserved for patients who present with a tumour. Surgical biopsy is usually only performed as part of a therapeutic operation.

Pituitary tumours

★ Overview

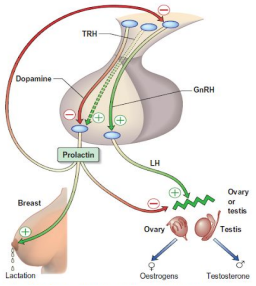
- Pituitary tumours are the most common cause of pituitary disease, and the great majority of these are benign pituitary adenomas, usually monoclonal in origin. **Symptoms arise as a result of:**
  - Local effects of a tumour: → Nonfunctional pituitary adenoma
  - or inadequate hormone production: → Hypopituitarism.
  - or excess hormone secretion (functional pituitary adenoma): The Types of secretory adenoma are:
    - GH secreting Adenoma → causing acromegaly in adults and gigantism in children.
    - Prolactin secreting adenoma → causing galactorrhoea or is clinically silent
    - ACTH secreting adenoma → causing Cushing's disease and Nelson's syndrome.
    - Rare TSH-, LH-and FSH-secreting adenomas.

★ Nonfunctional pituitary Mass

- **General Characteristics:**
  - Absence of signs and symptoms of hormonal hypersecretion.
  - 25 % of pituitary tumor.
  - Needs evaluation. Is it Microadenoma or Macroadenoma?
  - Average age 50 – 55 yrs, more common in males.
- **Presentation:**
  - Asymptomatic, incidentaloma[10] by MRI.
  - Macroadenoma could cause symptoms of **Mass effects:** (mechanical pressure or infiltration of surrounding structures)
    - Optic chiasm: causing a visual field defect (Bitemporal hemianopia).
    - Cavernous sinus with III, IV, VI, V_1 &V_2 cranial nerve lesions.
    - Bony structures and the meninges: causing headache.
    - Hypothalamic centres: Hypopituitarism, obesity, altered appetite and thirst, precocious puberty in children.
    - The ventricles: causing interruption of cerebrospinal fluid flow and hydrocephalus.
- **Hormonal findings:**
  - GH, LH, FSH, TSH, ACTH: not high.
  - PRL: low or high or normal. (**HOW?** depends on the size of adenoma, some are "totally silent" in that they result in neither hormonal excess nor clinical manifestations. BUT if it gets enlarged it may disrupt dopamine delivery to the pituitary by compression of the pituitary stalk, and consequently, be accompanied by a modest degree of hyperprolactinemia, in the late stage if the adenoma invades the hypothalamus tissue here the pt will get LOW PRL level).
- **Treatment:**
  - Observation:
    - Annual follow up for 5 years and then as needed.
    - Visual field exam Q6-12 months if close to optic chiasm.
    - Observe for a slow growing tumor.
  - Surgery: (Indicated if symptomatic, mass effect, etc)
  - Adjunctive Therapy: Radiation therapy to prevent regrowth of the remaining adenomatous.

[10] Such small lesions are sometimes detected during MRI scanning of the head for other reasons so-called 'pituitary incidentalomas'.

★ Functional pituitary Mass

1. Prolactin Secreting Pituitary Adenoma (Prolactinoma)	
Characteristic	• Most common of functional pituitary adenomas. • 25-30% of all pituitary adenomas • Some growth hormone (GH)-producing tumors also co-secrete PRL. • Prolactinomas women: 90% present with microprolactinomas • Prolactinomas in men: 60% present with macroprolactinomas • PRL is the only pituitary hormone that is inhibited by hypothalamus 
Diagnosis	**C: Clinical Features:** ○ In women: Hyperprolactinemia stimulates milk production in the breast producing galactorrhoea and nipple discharge[11], and inhibits GnRH causing oligo- or amenorrhoea & infertility[12]. ○ In men: Decreased libido, subfertility and erectile dysfunction in men. ○ If there is a pituitary tumour, there may be Mass-effect. ○ Ddx of prolactinoma: asleep[13], stress, pregnancy, lactation and chest wall stimulation or trauma, Renal failure, Liver failure Medication, hypothyroidism. ○ No clinical significance if there is no mass invading the hypothalamus. **B: Biochemical (hormonal):** • Prolactin level (a very high level suggests prolactinoma). • GH, LH, FSH, TSH, ACTH: normal or low. • TSH: to rule out Hypothyroidism (primary)[14]. • IGF-1: to rule out acromegaly co-secretion. **A: Anatomical:** CT or MRI of the pituitary[15]. • < 1 cm (microadenoma) • > 1cm (macroadenoma)
Treatment	1. Medical treatment is the first line (Dopamine agonist 'bromocriptine'[16]) It's not recommended for breastfeeding moms. 2. Surgical (if tumor is causing pressure symptoms)
DDx of hyperprolactinemia	**Pathological:** • The most common cause is a prolactin secreting pituitary adenoma (prolactinoma). • Other causes are primary hypothyroidism (high TRH levels stimulate prolactin). • Drugs which interfere with dopamine secretion or action: (Phenothiazines, metoclopramide, methyl-dopa, verapamil, H2 blocker, estrogen, opiates) **Physiological:** Mildly increased serum prolactin levels may be physiological and asymptomatic, could be due to: asleep, stress, pregnancy, lactation

[11] Spontaneous flow of milk unassociated with childbirth or breast feeding.
[12] which is why women present with microprolactinomas because they notice changes in their menstruation right away.
[13] Lack of sleep.
[14] Because high TRH levels as in 1ry hypothyroidism stimulate prolactin.
[15] MRI is superior to CT scanning and will readily show any significant pituitary mass.
[16] Not only will decrease the Prolactin level.. it will shrink the tumor also!

2. Growth Hormone Secreting Adenoma (Somatotropinoma)

Characteristic

- Represents 10% of pituitary adenomas
- It causes ACROMEGALY ضخامة الاطراف in adults, and GIGANTISM العملقه in children.
- Reduced overall survival by an average of 10 years.
- Causes:
  - Isolated, panhypopituitarism
  - Pituitary tumor as mass effect → Growth hormone deficiency

Diagnosis

C: Clinical Features:

- **Due to compression of surrounding structures** (usually large macro adenoma more than 1cm in size): Mass effects.

- **Due to invasion and destruction of the pituitary:** lack of secretion of other hormones.

- **Due to excess GH secretion**[17]**:**
  - Acral enlargement → large thick hands & feet
  - Soft tissue enlargement[18] → visceromegaly. Thick skin, oily and sweaty. Carpal tunnel syndrome[19]
  - Generalized symptoms, neuropathy: fatigue, lethargy & sleepiness.
  - Galactorrhea
  - Arthropathy: Arthralgia & degenerative arthritis.
  - **Impaired glucose tolerance,** glucose usually suppress the GH & diabetes (DM) because the GH has an anti insulin effect.
  - **Cardiovascular effects not reversible:**
    Cardiomegaly and CHF (Cardiac disease is a major cause of morbidity and mortality, 50 % died before age of 50) Diastolic dysfunction is an early sign of cardiomyopathy, HTN in 40%, LVH in 50%, Obstructive sleep apnea) HTN exacerbates LVH.
  - Have enlarged kidney which will absorb a lot of Na and water so they will present with **hypertension**.
  - Nitrogen retention and insulin antagonism and lipogenesis.
  - Increased risk of tumours like: colonic polyps and leiomyomata.

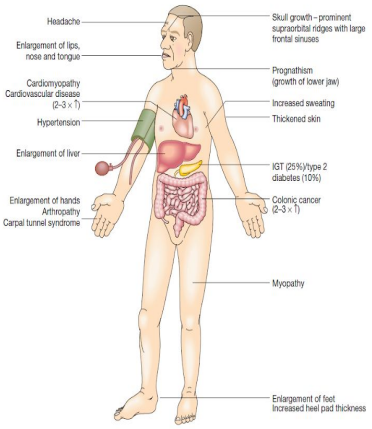


Fig. 20.29 Clinical features of acromegaly. (IGT = impaired glucose tolerance)

B: Biochemica(hormonal):

- Random GH level is not useful because there is wide physiologic fluctuation of GH levels[20].
- Screen(initial): measure IGF-1[21]
  → high in all patients with acromegaly, A normal serum IGF-1 concentration is strong evidence that the patient does not have acromegaly.
- Confirmatory Test: 75g oral Glucose tolerance test is diagnostic[22].
- Pituitary Function (LH, FSH, PRL, TSH, ACTH, cortisol, testosterone, T4).
- Fasting and random blood sugar, HbA1c, Lipid profile.

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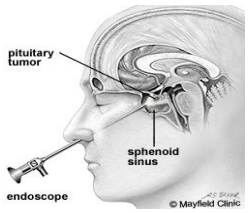
[17] If the GH is high before the epiphyses close the effect will be on the long bone and the person gets taller but if it occured after closure, the effect will be in small bone (enlarged feet and hand, prognathism فكه كبير).
[18] Enlargement in acral, face gross features, tongue Jaw.
[19] Because the tissue around the median nerve enlarge and compress the nerve the patient come with numbness typically at night.
[20] Sleeping is physiological stimuli to the GH, If you take a sample of blood from a child during sleep and the GH is low then there is problem. Usually the GH increase during sleep and after exercise.
[21] IGF-I is secreted from the liver under the control of GH, It's the easiest screening test.
[22] The GH is high and continue to be high during oral glucose tolerance test.

	A: Anatomical: ● MRI or CT for the pituitary ● Echo: Diastolic dysfunction as an early sign of cardiomyopathy ● Skull x-ray: thick heel pad ≥22mm
Treatment دائم يجي سؤال من هنا	1. First line therapy: Surgical (Trans-sphenoidal adenomectomy[23]) 2. Second line therapy: Somatostatin analogs or dopamine agonists. 3. Third line therapy: Somatostatin receptor antagonist. 4. Last resort: Radiotherapy[24] ○ Somatostatin analogues (octreotide) AKA (growth hormone inhibiting hormone) somatostatin inhibits the GH. ○ GH receptor antagonist (Pegvisomant) The goal is to lower the serum IGF-1 to normal for age and gender. 
DDx of Acromegaly	● 98% GH pituitary adenoma. ● Abuse of exogenous GH.

★ ACTH

- **HPA-axis:**
  - Circadian rhythm of cortisol secretion
    Altered by:
    - Physical stress
    - Psychological stress
    - CNS and pituitary disorder
    - Liver and renal failure
  - Early morning cortisol between 8-9 am

- **Cortisol low (Hypoadrenalism)**
  - Nausea, Vomiting, abdominal pain, Diarrhea
  - Dizziness and weakness, Tiredness, Muscle ache
  - Hypotension and Weight loss
  - Treatment: Cortisol replacement

3. ACTH secreting adenoma (Corticotropinoma)

ACTH adenoma → result in Cushing DISEASE

NOTE: Cushing's disease must be distinguished from Cushing's syndrome. cushing syndrome is a GENERAL term which refers to the abnormalities resulting from a chronic excess of glucocorticoids whatever the cause., whereas Cushing's disease specifically refers to excess glucocorticoids resulting from inappropriate ACTH secretion from pituitary adenoma.

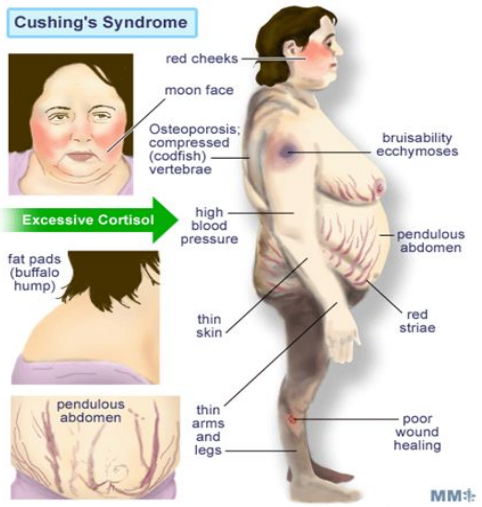
female diagnosed with SLE and she received corticosteroid so she will have cushing syndrome ,but cushing disease result from high ACTH release from anterior pituitary gland

[23] Access to the pituitary is achieved through the nasal cavity, sphenoid sinus and sphenoid bone. almost always surgery is done by a neurosurgeon **very very important.**

[24] Following the surgery. because the surgeon can't remove all the gland because he might remove the normal part so the patient continues with radiation.

C: Clinical Features important in exam: Related to excess cortisol (discussed in adrenal lecture)

- Moon face, central obesity, supraclavicular fat pad. (previously known as buffalo hump)
- Hirsutism[25] & acne.
- Stria that are Purple in color, thin skin that easily gets bruised → difficult IV cannulation, poor wound healing.
- DM.
- Irregular menstrual period. oligo or amenorrhea.
- Proximal muscle wasting and weakness.
- Recurrent infections, Cutaneous fungal infection.
- Depression.
- Osteoporosis with vertebral fracture → positioning of patient in OR (50 %), 20% with fracture.
- Cardiovascular effects (HTN, LVH, Diastolic dysfunction, Intra-ventricular septal hypertrophy)
- OSA[26]: 33% mild, 18% severe. Needs respiratory assessment and careful use of sedative during surgery
- Hypertension and hypokalemia.
- Thromboembolism.
- Glaucoma.



B: Biochemical: (discussed in adrenal lecture)

- High cortisol, high ACTH.
- 24hrs for Urinary Free Cortisol.
- 1mg Dexamethasone (the most potent corticosteroid) suppression test[27].
- Midnight salivary cortisol
- ACTH level and Pm cortisol

A: Anatomical:

- MRI
- ECG needed: high QRS voltage, inverted T-wave
- Echocardiogram pre-op

Treatment[28]:

- First line is Surgical
  1) Transsphenoidal surgery
     → if persistent (Pituitary irradiation) Radiation.
     → if persistent, Adrenalectomy:
     - Nelson's syndrome: expanding intracellular tumor and hyperpigmentation
- Medical (mitotane)

✓ Pregnancy:

First trimester: Surgery.
Second trimester: Adrenal enzyme inhibitors vs surgery.
Third trimester: Early delivery enzyme inhibitor until lung maturity.

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[25] Because the ACTH affect the zona reticularis which release androgen

[26] Obstructive sleep apnea

[27] اقول للمريض تعال العياده الساعه ١١ بالليل واعطيه doxamethasone واليوم الثاني الصباح اقيسه القاه عالي، المفروض انه يكون قل.

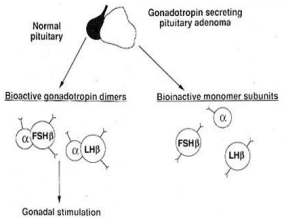
[28] In general it's always: **Surgical** then **Medical** then **Radiation** if nothing worked.

4. TSH secreting adenomas (Thyrotropinoma)

- Very rare < 2.8 %
- **Signs:** of hyperthyroidism (discussed in thyroid lecture)
- **Hormonal findings**[29]**:** High TSH, Free T4, Free T3
- **Treatment:**
    - Pre-op with anti-thyroid meds.
    - Surgical resection of adenoma.
    - Medical therapy: Somatostatin Analogue.

5. Gonadotropin secreting adenomas *Not imp for the MCQ and skipped by doctor

- Very rare
- **Clinical features**[30]
- **Hormonal findings:** hypersecretion of FSH, which is often accompanied by hypersecretion of FSH alpha-subunit (see the fig), less often by hypersecretion of LH.



- **How to know whether high FSH result from menopause or gonadotroph adenoma in women?** in gonadotroph adenoma there will be in addition to high FSH, high estradiol, thickened endometrium and\or polycystic ovaries.
- **Treatment:** First line is Surgery, to attempt to restore vision as quickly as possible, and then by radiation to prevent regrowth of the remaining adenomatous tissue.

★ Hypopituitarism

- **General Characteristics:**
    - Deficiency of hypothalamic-releasing hormones or pituitary hormones may be either selective or multiple. Multiple deficiencies usually result from tumour growth or other destructive lesions.
    - **Panhypopituitarism** is a deficiency of all anterior pituitary hormones. Vasopressin and oxytocin secretion will only be affected if the hypothalamus is involved by either hypothalamic tumour or by extension of a pituitary lesion.
- **Causes: (**Seven **I**'s)
    - **Infarction:** Sheehan's syndrome (pituitary infarction following severe postpartum haemorrhage)
    - **Iatrogenic:** Radiation, surgery
    - **Invasive:** Large pituitary tumors (most common cause), Craniopharyngioma.
    - **Infiltration:** Sarcoidosis, hemochromatosis (Fe deposition in pituitary).
    - **Injury:** head trauma
    - **Infections:** TB
    - **Idiopathic.**

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[29] 45 y\o Patient came to your clinic complaining of fatigue and increased sensitivity to cold and dryness of skin, what is the most likely diagnosis? Hypothyroidism. what tests you will order? T4, T3 and TSH.
If T4 and T3 are Low and TSH is high? → Problem is in the thyroid gland.
If T4 and T3 are Low and TSH is also Low? → Problem is in the pituitary gland.

[30] Typically present as middle-aged men who have a history of normal pubertal development and a normal fertility history, and by examination are normally virilized and have testes of normal size. They are brought to medical attention because of visual impairment, which is the result of the enormous size of the adenoma. while some patients have secondary hypogonadism because the adenomas are not secreting intact LH, but are compressing the normal gonadotroph cells and impairing LH secretion.

- **Clinical Picture of Hypopituitarism** (depends On Hormones Lost):
  - Lack of FSH LH → Hypogonadism: amenorrhea
  - Lack of TSH → hypothyroidism
  - Lack of ACTH → adrenocortical insufficiency
  - Prolactin deficiency → failure of postpartum lactation
  - Deficiency of GH → produces short stature in children
  - If all of the above → Panhypopituitarism

- **Investigations:** Testing Ant.Pit.Function (Each Axis Of The Hypothalamic–pituitary System Requires Separate Investigation):
  - Clinical: Hx and Px
  - Biochemical studies:
    - Baseline studies: TSH, ACTH, FSH, LH, prolactin, GH, Blood levels of IGF-1 may provide evidence of GH undersecretion.
    - Stimulation: TRH stimulation, GnRH(LHRH) stimulation, Insulin Tolerance Test (to Diagnosis ACTH and GH deficiency, in normal individual hypoglycemia will rise cortisol & Gh level)
  - **Imaging:** CT, MRI

- **Treatment:**
  - **Remove the cause.**
  - **Replacement Therapy (Depends On Hormone Lost):**
    - In secondary hypothyroidism give → Thyroxine
    - In secondary hypoadrenalism give → Hydrocortisone
    - GH deficiency give → GH analogues
    - Gonadotroph deficiency give → Testosterone monthly injections in men.
      Estrogen + progesterone in women.

      ➢ BUT If fertility is desired, give → LH and FSH analogues (For induction of ovulation in women, spermatogenesis in men)

1. Growth hormone deficiency	
C: Clinical	• ↓GH Function: Short stature. *The most common cause of short stature is related to genetics. • Mass-effect (mechanical pressure, hypopituitarism)

B: Biochemical	• Pituitary Function (LH, FSH, PRL, TSH, ACTH, Cortisol, Testosterone, T4)
	• Screen: IGF-1
	• Dynamic testing:
	  ○ Insulin tolerance testing.
	  ○ Clonidine stimulation test.
	  ○ Glucagon stimulation.
	  ○ Exercise testing.
	  ○ Arginine-GHRH.

A: Anatomical	• X-ray of hands: delayed bone age. • MRI.
Treatment	• GH replacement.

2. Central Hypothyroidism

- **C: Clinical**
  - Function : fatigue, weight gain, irregular menses, dry skin, depression, cold intolerance, increase sleep, slow thinking
  - O/E: obesity, Depressed face, eye brow
- **B: Biochemical:** Low T4 , Low TSH
- **A: Anatomical:** MRI
- **Treatment**
  - Thyroxine replacement
  - Surgical removal of pituitary adenoma if large

Particular syndromes related to hypopituitarism are: (Kumar)

- **Kallmann's syndrome:** Congenital deficiency of GnRH.
- **Pituitary apoplexy** سكته نخامية: Rapid enlargement of a pituitary tumour due to infarction or haemorrhage. There is severe headache and sudden severe visual loss, sometimes followed by acute life-threatening hypopituitarism
- **'Empty sella' syndrome:** radiologically the sella turcica (the bony structure that surrounds the pituitary) appears devoid of pituitary tissue. In some cases, the pituitary is actually placed eccentrically and function is usually normal. In others there is pituitary atrophy (after injury, surgery or radiotherapy) and associated hypopituitarism.

20.62 **Therapeutic modalities for 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	–	Radiotherapy may be more effective in children than in adults and appears to cause less hypopituitarism in the long-term
Craniopharyngioma	1st line	2nd line	–	

Hypothalamus & Posterior Pituitary Disorders

*The hypothalamus secretes vasopressor. This hormone goes to the distal convoluted tubule and collecting duct to make them absorb water. If this hormone is missed, the patient will have polyuria → Thirst (polydipsia)

Diabetes insipidus

Types	• **Central DI:** Decrease the amount of ADH
	• **Other types not related to hypothalamus pituitary disorders:**
	  ○ **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	• **Nephrogenic DI:** ↓ K, ↑ Ca, Lithium, Renal tubular acidosis, Sickle cell disease, Familial (mutation in ADH receptor).

	• **Central DI:**
	  ○ Disease of the hypothalamus: neurosurgery, head trauma, primary or secondary tumours, infiltrative disease (sarcoidosis, histiocytosis), vascular disease and 30-50% are idiopathic.
	  ○ Rare with sheehan's: mild, undetectable degree.
	NOTE: Damage to the hypothalamo-neurohypophysial tract or the posterior pituitary with an intact hypothalamus does not lead to ADH deficiency as the hormone can still 'leak' from the damaged end of the intact neuron.

Symptoms	Abrupt onset of polydipsia and polyuria.
Investigations	• **Urine:** ↑urine volume (3 – 20 L/day), ↓urine osmolality, ↓specific gravity • **Serum Na+:** usually high (bc ADH cause fractional excretion of Na in urine so lack of ADH result in high serum Na)

	Water deprivation test (To differentiate between CDI & NDI)
	Restrict p.o fluids or administer hypertonic saline to increase serum osmolality to 295-300 mosmol/kg (normal: 275-290).
	  ○ **Central DI:** urine osmolality still low (Before giving vasopressin) and returns to normal after administer vasopressin.
	  ○ **Nephrogenic DI:** exogenous vasopressin does not alter urine osmolality much.

Treatment	• **Central DI:** DDAVP (Desmopressin Acetate): Synthetic analog of ADH
	  ○ Not catabolized by vasopressinase → No vasopressor action
	  ○ Administered intranasally or p.o
	  ○ Titrate 10-20ug qd or bid
	  ○ Safe in pregnancy and breastfeeding
	• **Nephrogenic:**
	  ○ Correct underlying cause.
	  ○ Hydrochlorothiazide used to sensitize the renal tubules to endogenous vasopressin.
	• **Primary Polydipsia:** Psychiatric management.
	 

Syndrome Of Inappropriate Antidiuretic Hormone (SIADH)	
What is it	Continued ADH secretion in spite of plasma hypotonicity and a normal or expanded plasma volume.
Causes	SIADH is cCNS: meningitis, head trauma, tumors. 1. Pulmonary: Pneumonia,TB, small cell Ca (ectopic production of ADH). 2. Drugs: Chlorpropamide, Carbamazepine, Cyclophosphamide ,Vincristin.
symptoms	• There is nausea, irritability and headache with mild Dilutional hyponatremia. • Fits and coma may occur with severe hyponatremia.
Findings	• Low serum sodium (Hyponatremia) & ↑urinary sodium. • Low serum osmolality & ↑inappropriate urine osmolality.
Treatment	• Removal of underlying cause. • Restriction of fluid intake (0.5 – 1 L/day). • Demeclocycline. inhibits the action of vasopressin on the kidney.

	• If severe : I.V. hypertonic saline or normal infusion + Furosemide.

GH features:

1-Polypeptide hormone
2-Somatotrophs of anterior
3-Pituitary pulsatile secretion: variable level in the blood
4-Binds to its receptor on cell- surface: cytokine receptor
5-Lack intrinsic enzyme activity
6-Has similar receptor structure to others: leptin, IL-2, PRL
7-Controlled by HP and peripheral factors
8-GHRH stimulates it, somatostatin inhibits

↑↑ GH:
Physiologic: sleep, exercise, stress, fasting
Pathologic:Liver cirrhosis, AN, CRF, starvation
Pharmacologic: Estrogen, ACTH, ADH, GHRH, Ghrelin dopamine agonist, K infusion, serotonin arginin

↓↓ GH:
Physiologic: ↑glucose, ↑ FFAs,
Pharmacologic: Somatostatin, GH, GC, PG
Pathologic: ↑ or ↓ T4, Obesity

GH exerts its activity indirectly through the induction of insulin-like growth factor (IGF-1), which is synthesized in the liver and other tissues, or directly on tissues such as liver, muscle, bone or fat to induce metabolic changes)

The hypothalamus:

At the base of the brain, below third 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 Multiple nuclei in anterior part producing hormones to anterior pituitary Paraventricular and supraoptic nuclei produce ADH to control poster pituitary function

Function of the hypothalamus: The hypothalamus is the coordinator of Endocrine system.

- Receives signals from cortical brain, autonomic function, environment cues like light and temperature.
- Terminals of hypothalamic neurones 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.
- The hypothalamus pituitary axis: nonendocrine functions such as temperature regulation, the activity of the autonomic nervous system, and control of appetite.
- It affects function of thyroid gland, adrenal, gonads, growth, milk production and water balance

Summary

	Anterior Pituitary Disorders	Hypothalamus & Posterior Pituitary Disorders
Hypersecretion with/out mass effect	1- Prolactinoma: - High prolactinemia. - Presents with galactorrhea, decrease lipido and amenorrhea. **Tx: Medically** 2- GH Secreting Adenoma: - Causes acromegaly - Presents with DM, facial changes, CVD and Acral enlargement Tx: Surgery (1st line) 3- ACTH secreting adenoma - Result in **Cushing DISEASE.** - High cortisol, high ACH. - Presents with typical cushing features. Tx: surgery followed by radiation 4- TSH secreting adenomas - Rare - Present as usual hyperthyroidism - High T3,T4 and TSH 5- Gonadotropin secreting adenomas	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.
Non-functioning masses (incidentaloma)	Pituitary Adenomas, Pituitary incidentaloma, Craniopharyngioma, Metastatic tumours. which may present with normal hormonal level or mildly changed without manifestation	
Hyposecretion with/out mass effect	Deficiency of hypothalamic-releasing hormones or pituitary hormones Causes: (Seven **I**'s) - **Infarction** - **Invasive** - **Infiltration** - **Injury** - **Infections** - **Idiopathic** Clinical manifestation depends on the deficient hormone. 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.

Questions

1. A 15-year-old girl complains of headaches which started 6 weeks ago. The headaches initially occurred 1–2 times a week but now occur up to five times a week, they are not associated with any neurological problems, visual disturbances, nausea or vomiting. The girl also reports a white discharge from both of her nipples. She has not started menstruating. The most appropriate investigation is:

A. CT scan
B. Thyroid function tests
C. MRI scan
D. Serum prolactin measurement

2. 49-year-old man presents with a history of difficulty sleeping. He reports feeling increasingly tired and general weakness which he attributes to his poor sleep pattern. Additionally, the patient has noticed he has gained weight and sweats very easily. On examination, the patient has coarse facial features. The most likely diagnosis is:

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

3. A 47-year-old woman is referred to the endocrine clinic complaining of a two month history of tiredness. Despite wearing several items of clothing, the patient appears intolerant to the room temperature. She has noticed an increase in weight, particularly around her waist. The most appropriate investigation is:

A. Thyroid stimulating hormone (TSH)
B. Total tetraiodothyronine level (T4)
C. Tri-iodothyronine level (T3)
D. Ultrasound scan of the neck

Answers:

1. D / 2. C / 3. A