Pituitary disorders

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Objectives:

- introduction the concept of negative feedback mechanism
- Outline the anatomy and physiology of the hypothalamic pituitary axis
- Outline Hypothalamic hormones and their role
- Discussing Ant. Pituitary hormones and their stimuli
- Discussing Posterior pituitary hormones esp. ADH
- Causes of hyperprolactinemia
- Management of hyperprolactinemic states
- discussing acromegaly , its clinical manifestations and treatment
- Discussing hypopituitarism, its clinical presentation, causes and management.
- Introducing the subject of diabetes insipidus and the syndrome of inappropriate ADH secretion

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References:

Slides - Black

Doctor' s notes - Orange

Important - Red

Step up /cecil / davidson - Blue

Extra explanation - Grey

Editing file

Optional:

p787 to p795

❖ Introduction: anatomy and physiology of the pituitary gland

All releasing hormones are stimulatory except:

Dopamine inhibits prolactin, somatostatin inhibits growth hormone

Anatomy:

- **Anterior pituitary is recognizable by 4- 5th wk of gestation**
- **Full maturation by 20th wk**
- **From Rathke's pouch, Ectodermal evagination of oropharynx**
- **Migrate to join neurohypophysis**
- **Portion of Rathke's pouch →→ Intermediate lobe**
- **Remnant of Rathke's pouch cell in oral cavity →→ pharyngeal pituitary**
- **Lies at the base of the skull above <u>sella turcica</u>**
- **Roof is formed by diaphragma sellae**
- **Floor by the roof of sphenoid sinus**

Diaphragma sellae is formed by a reflection of dura matter preventing CSF from entering the sella turcica by this diaphragm

- **Pituitary stalk and its blood vessels pass through the diaphragm**
- **Lateral wall by cavernous sinus containing III, IV, VI, V1, V2 cranial nerves and internal carotid artery with sympathetic fibers. Both adjacent to temporal lobes**
- **Pituitary gland measures 15 X 10 X 6 mm, weighs 500 mg but about 1 g in women**
- **Optic chiasm lies 10 mm above the gland and anterior to the stalk**
- **Blood supply : superior, middle, inferior hypophysial arteries (internal carotid artery) running in median eminence from hypothalamus**
- **Venous drainage: to superior and inferior petrosal sinuses to jugular vein**

Physiology: it Is divided into: Anterior & Posterior

- The anterior pituitary gland, regulated by the hypothalamus, produces six tropic hormones which control the functioning of other organs.
- The posterior pituitary stores hormones produced by the hypothalamus and releases them into the bloodstream

Anterior lobe (adenohypophysis) true gland, secretes hormones	**Posterior lobe (neurohypophysis):** connected to hypothalamus, stores hormones secreted by hypothalamic nuclei
GH: Released by GHRH, sleep, stress, exercise, hypoglycemia, clonidine (α2 agonist)	**Oxytocin: Uterine contractions; milk let-down**
Prolactin: When there is interference with dopamine action or secretion, pregnancy & lactation	**ADH (Vasopressin): Water balance**
ACTH: Increased by CRH, stress	
TSH: Increased by TRH stimulation	
FSH&LH: Increased by stimulation from GnRH	

FSH: in men, stimulates testicular growth and spermatogenesis. In women, it stimulates follicular growth production of estrogen & progesterone

LH: stimulates ovulation in women and testosterone production in males

❖ 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.
- 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

❖ Hypothalamic pituitary axis

- The hypothalamus is the coordinator of Endocrine system
- Received signals from cortical brain, autonomic function, environment cues like light and temperature
- It affects function of thyroid gland, adrenal, gonads, growth, milk production and water balance
- Non-endocrine functions such as temperature regulation, the activity of the autonomic nervous system, and control of appetite.

❖ HYPOPITUITARISM

Hypothalamus and pituitary
6;34 min

❖ Definition:

Hypopituitarism: deficiency in pituitary hormones production.
Panhypopituitarism: all hormones of pituitary gland can't be secreted

❖ Causes: 7Is

1. **Infarction: Sheehan's syndrome[1].**
   - **This occur only when pituitary gland is enlarged (like in pregnancy).**
   - **Any change in BP or circulation causes infarction of enlarged pituitary gland, while this isn't occurring in people with normal sized pituitary gland.**
   - **e.g. If pregnant woman during delivery lost big volume of blood = decrease BP = infarction of pituitary gland = hypopituitarism. Why? because pituitary gland during pregnancy is big.**
     - **Posterior lobe of pituitary won't affect by the infarction (so no cases with diabetes insipidus)**
2. **Iatrogenic: Radiation, surgery**
3. **Invasive: Large pituitary tumors (CRANIOPHARYNGIOMA)**
4. **Infiltration: Sarcoidosis, hemochromatosis**
5. **Injury: head trauma**
6. **Infections: TB**
7. **Idiopathic.**

❖ Clinical manifestations: Depends on hormones lost

1. **Lack of FSH, LH: Hypogonadism: amenorrhea.**
2. **Lack of TSH: hypothyroidism.**
3. **Lack of ACTH: hypoadrenalism: adrenocortical insufficiency**
4. **Prolactin deficiency: failure of postpartum lactation, so it is only evident at time when it is needed (during lactation) otherwise unnoticeable.**
5. **In children: GH > short stature.**
6. **If all of the above: Panhypopituitarism**

1. Sheehan's syndrome is a condition that affects women who lose a life-threatening amount of blood in childbirth or who have severe low blood pressure during or after childbirth, which can deprive the body of oxygen. In Sheehan's syndrome, the lack of oxygen can damage your pituitary gland.

❖ Diagnosis:

- **Clinical: History and Physical examination.**
- **Biochemical studies:**

Testing anterior pituitary function by hormones stimulations

- **Insulin (to induce hypoglycemia): expected to increase GH and ACTH.**
- **TRH: expected to increase TSH and small amount of prolactin.**
- **GnRH: expected to to increase FSH&LH.**

All are given at the same time.

Then measure the hormones (after 2 hours), If they are low this confirmed diagnosis.

- **Radiological: MRI, CT**
  - **If there is a tumor suspicion.**

❖ Treatment:

- **Treat the underlying cause.**
- **Replacement therapy; depends on hormone lost**
  - **Thyroxine: in secondary hypothyroidism.**
  - **Hydrocortisone: in secondary hyperadrenalism.**
  - **GH: for children.**
  - **Testosterone: monthly injections.**
  - **Estrogen + progesterone.**
  - **Gonadotropin (FSH + LH): For induction of ovulation in women and for induction of spermatogenesis in men.**

❖ Hyperprolactinemia

Anything that interfere with dopamine would rise the prolactin level

❖ Causes:

- Prolactinoma. (prolactin secreting adenoma), most common cause of hyperprolactinemia
- Hypothyroidism. There is an increased TRH as compensation → ↑Prolactin secretion
- Medications. All medication that can interfere with dopamine, for example: phenothiazine(antipsychotic), metoclopramide(antiemetic), methyl-dopa(used for hypertension in pregnant women) verapamil, H2 blockers, Estrogen, OPiates, dopamine receptor antagonists, reserpine)
- Pregnancy (estrogen increase).
- Renal failure. the kidney is unable to excrete the prolactin so it stays in the blood
- Chest wall burns - neurona effect like suckling
- Idiopathic.

❖ Clinical features

♀	• galactorrhea (lactation in the absence of breastfeeding) • amenorrhea or oligomenorrhea (absence of menstrual bleeding or decreased in the number of menstrual cycle per year) • Hypogonadism • infertility How amenorrhea happens? when the prolactin is high, it interferes with the gonadotropic secretion.
♂	• Decreased libido • infertility • impotence • galactorrhea or gynecomastia (uncommon) • Hypogonadotropic Hypogonadism

❖ Diagnosis:

- Hormonal: elevated serum prolactin level (if it was very high, it suggests prolactinoma)
- Radiological: in prolactinoma: CT or MRI of the pituitary (>1cm macroadenoma), (<1cm microadenoma)

Order a pregnancy test and TSH level, because both pregnancy and primary hypothyroidism are on the differential diagnosis of hyperprolactinemia

❖ Treatment:

Treat the underlying cause (stop medication if possible, treat hypothyroidism)

- Medical: bromocriptine, cabergoline (dopamine agonist)
- Surgical: if treatment management is failed

MRI is the best test to diagnose a hyperprolactinemia due to a pituitary adenoma

❖ Prolactinomas

- most common functional pituitary tumor
- 10% are lactotroph and somatotroph such as GH producing
- Presents with amenorrhea and infertility
- Prolactinomas lose TRH response
  - Microadenomas <10mm on MRI
  - Macroadenoma >10mm

❖ Syndrome of inappropriate ADH (SIADH)

❖ Pathophysiology: Elevated levels of ADH lead to water retention and concentrated urine. This has two major effects: hyponatremia & volume expansion.

People with SIADH will have Water retention and hyponatremia. Although they have volume expansion, they DO NOT develop edema. [Euvolemic hyponatremia]

Anything would injure the hypothalamic-pituitary axis (eg: Trauma, tumor, infections) could give either SIADH OR DI!

❖ Causes:

- Neoplasms:(lung, prostate, pancreas, bladder), lymphomas, leukemia
- CNS: meningitis, head trauma, tumors
- Pulmonary: pneumonia, TB, small cell carcinoma
- Drugs: Chlorpropamide (sulfonylurea antidiabetic), Carbamazepine (anticonvulsant), Cyclophosphamide (antineoplastic), vincristine(antineoplastic)

❖ Clinical presentation:

confusion, nausea, irritability, fits(seizures), coma

Clinical manifestation of SIADH will be exact the same as those who are in hyponatremic state (CNS manifestation)

❖ Treatment:

- removal of underlying cause
- restriction of fluid intake (0.5 – 1 L/day)
- Demeclocycline. Lithium also can be used. However, it has more side effect
- If severe: I.V. hypertonic saline or normal infusion + Furosemide

Don’t raise the serum sodium concentration too quickly. Rapid flux of water into the ECF can result in central pontine myelinolysis! (demyelination syndrome may result)

❖ Growth hormone

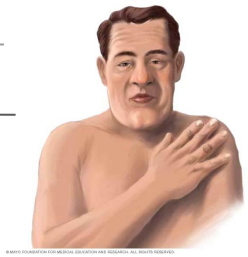
- Polypeptide hormone
- Somatotrophs of anterior pituitary
- Action is mediated by IGF-I
- Half life is 20-50 mins
- Has a binding protein: GHBPs
- Pulsatile secretion: variable level in the blood
- Binds to its receptor on cell- surface: cytokine receptor
- Lack intrinsic enzyme activity
- Has similar receptor structure to others: leptin, IL-2, PRL
- Controlled by HP and peripheral factors
- GHRH stimulates it, somatostatin inhibits

Growth hormone deficiency investigation:

- ❑ **Basal test:**
  - GH level
  - IGF-1 level
- ❑ **Dynamic test:**
  - insulin tolerance testing
  - Clonidine stimulation test
  - glucagon stimulation
- ❑ **Imaging:**
  - Hands X-ray
  - MRI pituitary
- ❖ **Management: GH replacement**

- **Factors that:**

↑↑ GH	↓↓ GH
• **Physiologic:** sleep, exercise, stress, fasting • **Pathologic:** Liver cirrhosis, CRF*, starvation • **Pharmacologic:** Estrogen, ACTH, ADH, GHRH,Ghrelin dopamine agonist, K infusion,serotonin, arginine	• **Physiologic:** ↑glucose, ↑ FFAs, • **Pharmacologic:** Somatostatin, GH,GC, PG • **Pathologic:** ↑ or ↓ T4, Obesity



ACROMEGALY

Acro: limbs, megaly: enlargement

❖ Definition:

Acromegaly is overproduction of growth hormone leading to soft tissue (Skin, Connective tissue, cartilage, bone and viscera) overgrowth throughout the body.

- **In childhood it is called gigantism.**
- **It's not a common condition (one case yearly)**
- **High mortality rate because of diabetes and its effect on CVS (cardiomegaly, secondary HTN)**
- **Produced by GH producing adenoma where there is Increase GH production**

- **If this occur before closing of epiphyses (before the puberty) the patient will become long stature (no limitation for increase the height) this is called gigantism.**
- **If it occurs after closing of epiphyses (after puberty) it will effect on small bones making them huge (stature doesn't change).**

❖ Risk s of long term excess GH

- Arthropathy
- Neuropathy
- Cardiomyopathy
- Respiratory Obstruction
- Diabetes mellitus
- Hypertension: exacerbates Cardiomyopathy (not reversible)
- increase risk of tumors: leiomyoma and colon polyps
- Reduce overall survival by an average of 10 years

98% GH pituitary adenoma
⅓ of all functional pituitary adenomas
nitrogen retention, insulin antagonism and lipogenesis

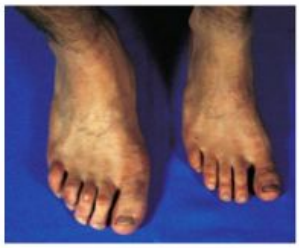
CRF = Chronic renal failure / FFAs = Free Fatty Acids / GC = Glucocorticoid-Inducible Glutamine Synthetase

❖ Clinical manifestations:

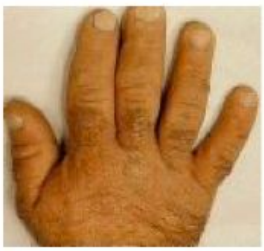
classified into 3 based on the following:

Large tumor (macroadenoma) more than 1 cm in size	Invasion and destruction of the pituitary	Increased GH production
• Frontal headache • Dizziness • Bitemporal hemianopia: due to compression of optic chiasma by the huge tumor.	Tumor invades other normal cells within gland that produce ACTH, TSH, gonadotropin. lack of secretion of these hormones. Therefore, they will be deficient. That's why Acromegalic patient might complaining of secondary hypothyroidism and hypoadrenalism	• Big hands, jaw, macroglossia (big tongue) and cartilage. Increase in all body tissues result in: • Carpal tunnel syndrome due to compression of median nerve by the tissue. • Cardiomegaly and CHF patient might. • Colonic polyp. • Thick sweaty skin. • Body odor: due to Increase number and size of Sebaceous glands that secret the sebum. • Amplified voice: Due to Maxillary sinus become bigger Generalized symptoms: fatigue , lethargy & sleepiness. • Arthralgia & degenerative arthritis. • Impaired glucose tolerance & diabetes. • Erectile dysfunction from increased prolactin consecrated with pituitary adenoma.

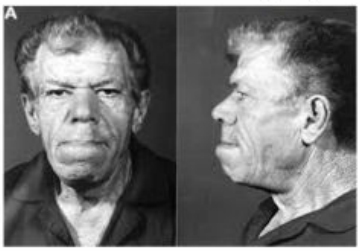
Classic features of acromegaly



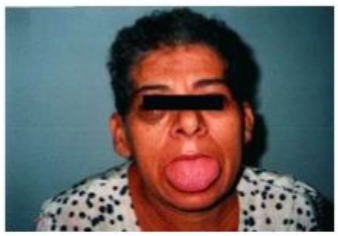
Increase in shoe size



Increase in ring size



Increase in hat size



Macroglossia (big tongue)

❖ Diagnosis:

1. Measure IGF-1	2. Glucose suppression test (Measure GH during OGTT[1])	3. Radiological diagnosis
• **Best initial** • GH induces secretion of IGF-1 from the liver so it used to reflect the level of GH. • IGF-1 acts as mediator of growth hormone's anabolic effects.	• **Most accurate.** • Normally glucose suppress GH levels, so insulin induced hypoglycemia increases level of GH (GH: glucose) **Oral glucose tolerance test**: يجي المريض بكرة صايم ثم اعطيه محلول سكر ثم بعد ساعتين اسحب عينه • In normal people.GH become undetectable. If there is a tumor GH will be high despite the injection of glucose.	**MRI done only after laboratory identification.**

To differentiate between acromegaly from normal big man is by ask to bring old picture for him when he was younger to do a comparison.

❖ Treatment:

- 1st choice. Surgical (trans-sphenoidal resection):
- 2nd:Somatostatin analogues (octreotide or lanreotide) or dopamine (cabergoline):
  - If there is residual after surgery.
  - To reduce GH production.
- 3rd: GH receptor antagonist (Pegvisomant). To inhibits IGF release from the liver.
- Last resort: Radiation

❖ **Goals of the treatment:** (Isn't cosmetic and tall patient will not become short)

- To Protect the heart (Heart size will be improved and becomes normal after few years).
- To treat secondary HTN (high level of GH increases salt and water reabsorption by the kidney)
- Some hormones like cortisol, catecholamine and GH oppose the action of insulin, so after treatment glucose tolerance will be improved therefore diabetes will disappear.

1.Oral glucose tolerance test

❖ DIABETES INSIPIDUS (DI)

❖ Definition:

Diabetes insipidus is decrease in either amount of ADH from the pituitary (central DI) or its effect on kidney (nephrogenic DI).

❖ Etiology:

Central	Nephrogenic
• **Abrupt onset** • **ADH; hypothalamus is not producing ADH for several causes such as tumor, head trauma, vascular, hypoxia, surgery, infiltration, infection or could be idiopathic.** • **Rare with Sheehan's (mild, undetectable degree)** • **Polydipsia and polyuria (1-15 L/day)** **Diagnosis of central DI:** • **Restricted p.o fluids or administer hypertonic saline to increase serum osomlarity to 295-300 mosmol/kg** • **urine osmolarity return to normal after administer vasopressin**	• **A few kidney diseases such as chronic pyelonephritis, amyloidosis, myeloma, sickle cell disease will damage the kidney enough to inhibit the effect of ADH.** • **Hypercalcemia and hypokalemia inhibit ADH effect on the kidney** • **Lithium is a classic cause of NDI (nephrogenic DI)**

❖ Clinical manifestations:

Patient every hour goes to the bathroom to urinate even at night, after that he will drink water to compensate what he lost. If he doesn't drink he will collapse.

Polydipsia & Polyuria:	Hypernatremia:
↑ urine volume (3 – 20 L/day) **↓ urine osmolality** **↓ specific gravity**	**If it is severe, there will be some neurological symptoms such as confusion, disorientation, lethargy, and eventually seizure and coma. Neurological symptoms occur only when volume losses aren't matched with drinking enough fluid.**

❖ Diagnosis:

- **↑ Serum Na (serum osmolality is elevated).**
- **↓ Urine Na and osmolality.**
- **Urine volume is enormous.**
- **Difference between central and nephrogenic DI is determined by the response to ADH (vasopressin stimulation test)**

❖ Treatment:

- **Desmopressin stimulation test:**
  - **Urine:**

(volume decreased + osmolality increased = central DI)

★ **Give desmopressin.**

  - **Urine: no effect = nephrogenic DI**

★ **Treat underlying cause.**

★ **Give hydrochlorothiazide, amiloride, NSAIDs.**

Desmopressin:

- **Not catabolized by vasppressinase**
- **No vasopressor action**
- **Safe in pregnancy and breastfeeding**

❑ **Primary Polydipsia:**

- **psychiatric management**

NOT Important

Summary for the extra female slides

Pituitary adenoma can affect all pituitary hormones other than (prolactin, GH)

- It can comes as
  - Mass effect (eg: visual abnormality)
  - Overproduction (eg: TSH-secreting, ACTH-secreting.. etc)
  - Hypopituitarism [Non-functioning adenoma]. (eg: Gonadotrophin adenoma)

TSH – secreting adenoma

- **An increase in T4, T3 as a result of ↕ TSH**
- **Clinical presentation:** Mild signs and symptoms of hyperthyroidism
  - Symptoms: Palpitations, tremor, weight loss, diarrhoea, heat intolerance, irregular period in female, excessive sweating
  - Signs: tachycardia, tremor, warm skin, goiter sometimes
- **Surgical Management:** Transsphenoidal surgery
- **Medical Management:**
  - **Dopamine Agonist**
  - **Somatostatin analogue (Octreotide)**

Gonadotrophin adenoma

- **usually comes with decrease in FSH, LH**
- **Surgical Management:** Transsphenoidal surgery
- **Medical Management:**
  - **Male:** Testosterone
  - **Female:** Oestrogen

Other disorders of pituitary:

- **Infiltrative lesions**
  - Hereditary Hemochromatosis
  - Fe (Iron) deposition in pituitary
  - Gonadotropin deficiency most common
  - Treatment: Repeat phlebotomy
- **Pituitary apoplexy**
  - sudden hemorrhage into pituitary
  - severe, sudden Headache, diplopia and hypopituitarism
  - **sudden ACTH deficiency cause life threatening hypotension**
  - Treatment: Surgical decompression

MCQ's

Q1: A 45-year-old man comes to the physician because his "face and voice have changed." The patient came to this realization after meeting a nephew, who had not seen him for 2 years and could hardly recognize him. He also reports that he has had persistent joint pains in the past 6 months. His blood pressure is 140/90 mmHg, but he says he has never had values over 120/80 mmHg on previous health maintenance examinations. Physical examination reveals coarse facial features, a large tongue, and thick fingers. His handshake is moist and doughy, and his voice deep. Which of the following is the most appropriate next step in diagnosis?

(A) CT scans of the head
(B) MRf of the head
(C) Measurement of baseline growth hormone levels
(D) Measurement of growth hormone levels following glucose suppression test
(E) Measurement of TSH levels

Q2: A 30-year-old woman goes to her physician complaining of a whitish discharge from her nipples for the past 3 months. She denies headaches or visual problems. She notes that she often feels tired but attributes it to the feet that she has to take care of her 18-month-old daughter. She has not had a menstrual period since her delivery and has not nursed her baby for the past 5 months. She is not taking any medications. Her physical examination is unremarkable. She does not have any visual field defects. Laboratory results show a prolactin level of 200. Which of the following is the most appropriate next step in diagnosis?

(A) Chest x-ray film
(B) CT scan of the brain
(C) Measurement of thyroid hormone levels
(D) No additional investigation is warranted
(E) Pregnancy test

Q3: 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. Lateral skull x-ray
B. CT scan
C. MRI scan
D. Thyroid function tests
E. Serum prolactin measurement

Q4: A 69-year-old man presents with confusion. His carers state that over the last month he has become increasingly lethargic, irritable and confused. Despite maintaining a good appetite, he has lost 10kg in the last month. Blood results are as follows:

- **Sodium 125 mmol/L**
- **Potassium 4 mmol/L**
- **Urea 3**
- **Glucose (fasting) 6 mmol/L**
- **Urine osmolality 343 mmol/L**

The most likely diagnosis is:

A. Hypothyroidism
B. Dilutional hyponatraemia
C. Addison's disease
D. Acute tubulointerstitial nephritis
E. Syndrome of inappropriate antidiuretic hormone (SIADH)

Answers: 1.D, 2.E, 3.E, 4.E

Thank you

If you have any question please contact with us at:
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