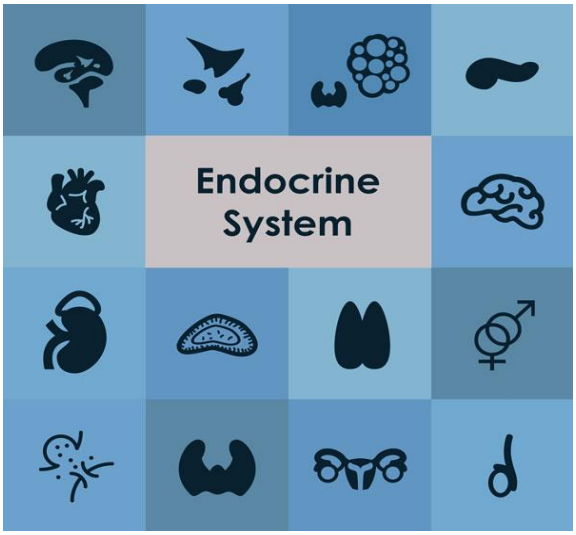
BAU-Medicine



Sheet no. 1

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Lecture Title: Diseases of pituitary gland part 1.

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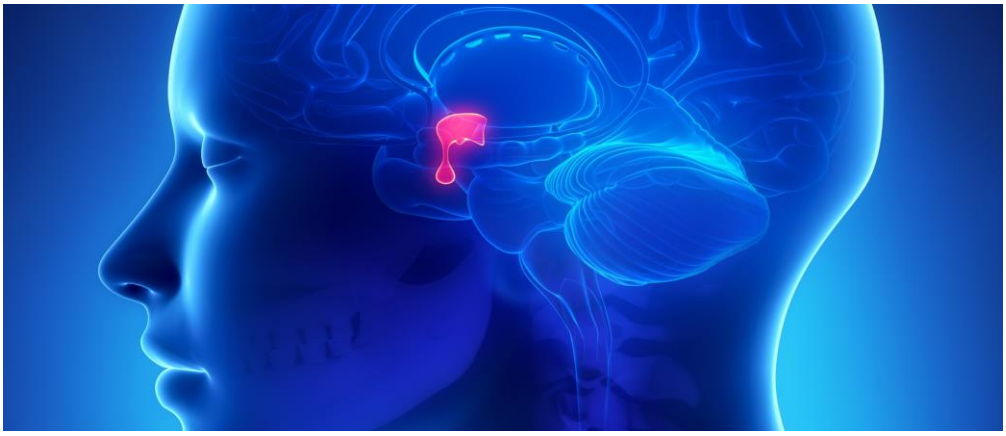
دعاء لأخينا رشيد

اللهمّ آته برحمتك ورضاك، وقهِ فتنة القبر وعذابه، وآته برحمتك الأمن من عذابك حتّى تبعثه إلى جنّتك يا أرحم الرّاحمين



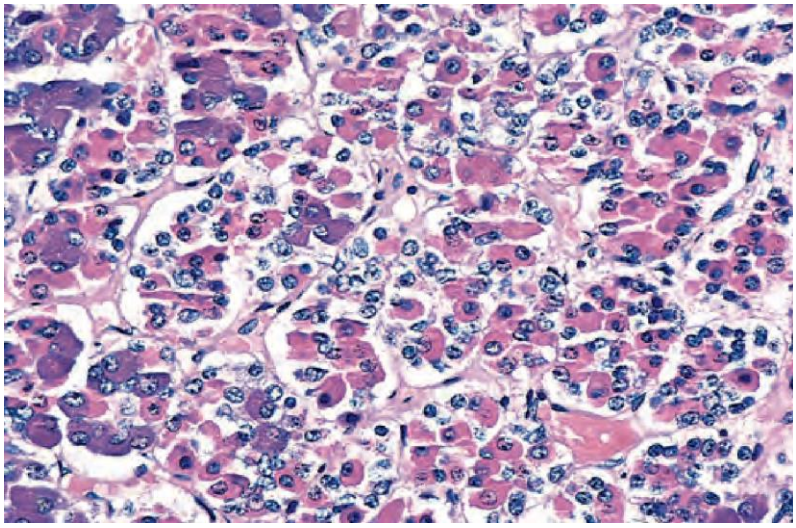
❖A brief introduction:

- Anterior lobe of the Pituitary gland is called the Adenohypophysis.
- Posterior lobe of the Pituitary gland is called the Neurohypophysis.

- ➢ Most of the hormones we will discuss are mostly secreted by the anterior lobe of the pituitary gland, the production of most anterior pituitary hormones is controlled mainly by the positively (Stimulatory) and negatively (inhibitory) acting factors from the Hypothalamus.
- ➢ The posterior pituitary acts as a storage for the hormones produced by the Hypothalamus (ex: Antidiuretic hormone (Vasopressin), Oxytocin).
- ➢ Normal histology of anterior pituitary:
  3 types of cells according to cytoplasmic staining
  Acidophils-Basophils-Chromophobes (Cytoplasm is not stained).
  For example:
  -Lactotrophs: Acidophilic.
  -Corticotrophs: Basophilic.

Sheet notes:

- ❖ Notice between the cells that there is a Reticulin fiber network (Collagen type III).
- ❖ Adenoma: no reticulin fiber network.
- ❖ Hyperplasia: reticulin fiber network is still present but the number of cells has increased.



❖ 6 terminally differentiated cell types in the anterior pituitary:

- **Somatotrophs**, producing growth hormone (GH).
- **Mammosomatotrophs**, producing GH and prolactin (PRL).
- **Lactotrophs**, producing PRL.
- **Corticotrophs**, producing adrenocorticotropic hormone (ACTH) and pro-opiomelanocortin (POMC), Melanocyte-stimulating hormone (MSH).
- **Thyrotrophs**, producing thyroid-stimulating hormone (TSH).
- **Gonadotrophs**, producing follicle-stimulating hormone (FSH) and Luteinzing hormone (LH).

Sheet notes:

❖ POMC is a precursor protein that gives rise to 3 other proteins:

1. ACTH.
2. MSH.
3. Endorphins (endogenous opioids).

❖ The posterior pituitary:

- Similar to neural tissue.
- Made up of Pituicytes (modified glial cells) and axon terminals (from the axons that extend from the hypothalamus through the pituitary stalk).
- Oxytocin and Vasopressin (ADH) are peptide hormones synthesized in the hypothalamus and stored in the axon terminals.

Sheet notes:

❖ Oxytocin is important for uterine contractions (during labor) and the suckling reflex (for breast feeding).

❖ Vasopressin acts as an antidiuretic (ADH).

❖ Clinical manifestations of anterior pituitary disease:

- **Hyperpituitarism:**

  Adenoma: **benign** neoplasm of pituitary cells.

  Due to:

  -Anterior pituitary hyperplasia, adenoma-functional- (most common cause) or carcinoma.

  -Secretions from non-pituitary tumors (ectopic hormones secreted from Non-pituitary tumors) for example a paraneoplastic syndrome such as cushing syndrome (ACTH produced by Small Cell Lung Carcinoma or carcinoid).

- **Hypopituitarism :**

  Due to:

  -Destruction of anterior pituitary (ischemia, surgery, radiation, inflammation).

  -Nonfunctional pituitary adenomas (don't secrete hormones).

  Sometimes a nonfunctional adenoma might compress and take place over the other healthy parts of the pituitary gland causing hypopituitarism.

- **Local mass effects: (due to large pituitary tumors)**

  -This can be seen as a radiographic abnormality of the sella turcica (sellar expansion, bony erosion or diaphragm sella disruption).

  -Bitemporal hemianopsia (loss of vision) due to the compression on the optic chiasm, also there are some nonspecific visual abnormalities.

  -Elevated intracranial pressure (headache and vomiting).

  -In certain cases, sudden hemorrhage in an adenoma might cause sudden enlargement this is called pituitary apoplexy and it's a Neurologic emergency.

  -Occasionally may cause hypopituitarism, the tumor might compress part of the stalk that connects the hypothalamus to the anterior pituitary gland causing a decrease in stimulation → hypopituitarism.

❖ Pituitary adenomas:

- The most common cause of hyperpituitarism is: functional pituitary adenoma.
- Usually adults (35-60 years old).
- Microadenomas (<1cm) and Macroadenomas if larger.
- Nonfunctional adenomas are likely to come to clinical attention at a later stage than those associated with endocrine abnormalities are therefore most likely to be macroadenomas (cause mass effect).
- In 14% of autopsies have silent microadenomas (clinically silent) and they are discovered incidentally (by imaging or autopsy) hence the name (incidentaloma).

- Functional adenomas such as prolactinoma and corticotroph adenomas cause symptoms (endocrine abnormalities) so they are detected faster and earlier (detected as microadenomas).

❖ Classification of pituitary adenomas:

Pituitary Cell Type	Hormone	Adenoma Subtypes	Associated Syndrome*
Lactotroph	Prolactin	Lactotroph adenoma Silent lactotroph adenoma	Galactorrhea and amenorrhea (in females) Sexual dysfunction, infertility
Somatotroph	GH	Densely granulated somatotroph adenoma Sparsely granulated somatotroph adenoma Silent somatotroph adenoma	Gigantism (children) Acromegaly (adults)
Mammosomatotroph	Prolactin, GH	Mammosomatotroph adenomas	Combined features of GH and prolactin excess
Corticotroph	ACTH and other POMC-derived peptides	Densely granulated corticotroph adenoma Sparsely granulated corticotroph adenoma Silent corticotroph adenoma	Cushing syndrome Nelson syndrome
Thyrotroph	TSH	Thyrotroph adenomas Silent thyrotroph adenomas	Hyperthyroidism
Gonadotroph	FSH, LH	Gonadotroph adenomas Silent gonadotroph adenomas ("null cell," oncocytic adenomas)	Hypogonadism, mass effects, and hypopituitarism

- This classification is according to immunohistochemical staining (not overproduction of the hormone in the blood meaning it can be function or nonfunctional).
- Some pituitary adenomas can secrete 2 hormones (GH and Prolactin being the most common combination) this is seen in a Mammosomatotroph, and rarely, pituitary adenomas are plurihormonal (more than 2 hormones).
- Pituitary adenomas can be functional (associated with hormonal excess and clinical manifestations) or nonfunctional (without clinical symptoms of hormone excess).
- Large pituitary adenomas, and particularly nonfunctional ones (Macroadenomas) may cause hypopituitarism by encroaching on and destroying the adjacent anterior pituitary parenchyma.

❖ Pituitary adenomas, molecular pathology:

Gene	Protein Function	Mechanism of Alteration	Most Commonly Associated Pituitary Tumor
Gain of Function			
GNAS	GNAS encodes for alpha subunit of stimulatory G-protein, Gsα. Oncogenic mutation of GNAS constitutively activates Gsα, leading to upregulation of intracellular cyclic AMP (cAMP) activity	Activating mutation	GH adenomas
Protein kinase A, regulatory subunit 1 (PRKAR1A)*	*PRKAR1A* encodes for a negative regulator of protein kinase A (PKA), a downstream mediator of cAMP signaling. Loss of PKA regulation leads to inappropriate cAMP activity	Germline inactivating mutations of *PRKARIA* are present in autosomal dominant Carney complex	GH and prolactin adenomas
Cyclin D1	Cell cycle regulatory protein; promotes G1-S transition	Overexpression	Aggressive adenomas
HRAS	Ras regulates multiple oncogenic pathways including proliferation, cell survival and metabolism	Activating mutation	Pituitary carcinomas rare
Loss of Function			
MEN1*	MEN1 encodes for menin, a protein with protean roles in tumor suppression, including repression of oncogenic transcription factor JunD, and in histone modification.	Germline inactivating mutations of *MEN1* (multiple endocrine neoplasia, type 1)	GH, prolactin, and ACTH adenomas
CDKN1B (p27/KIP1)*	The p27 protein is a negative regulator of the cell cycle	Germline inactivating mutations of CDKN1B ("MEN-1-like" syndrome)	ACTH adenomas
Aryl hydrocarbon receptor interacting protein (AIP)*	Receptor for aryl hydrocarbons and a ligand-activated transcription factor	Germline mutations of *AIP* cause pituitary adenoma predisposition [PAP] syndrome	GH adenomas (especially in patients younger than 35 years of age)
Retinoblastoma (RB)	Retinoblastoma protein is a negative regulator of the cell cycle (Chapter 7)	Methylation of *RB* gene promoter	Aggressive adenomas

Elsevier. Kumar et al. Robbins and Cotran pathologic basis of diseases 9th...

The doctor said he only wants the things that are outlined in black.

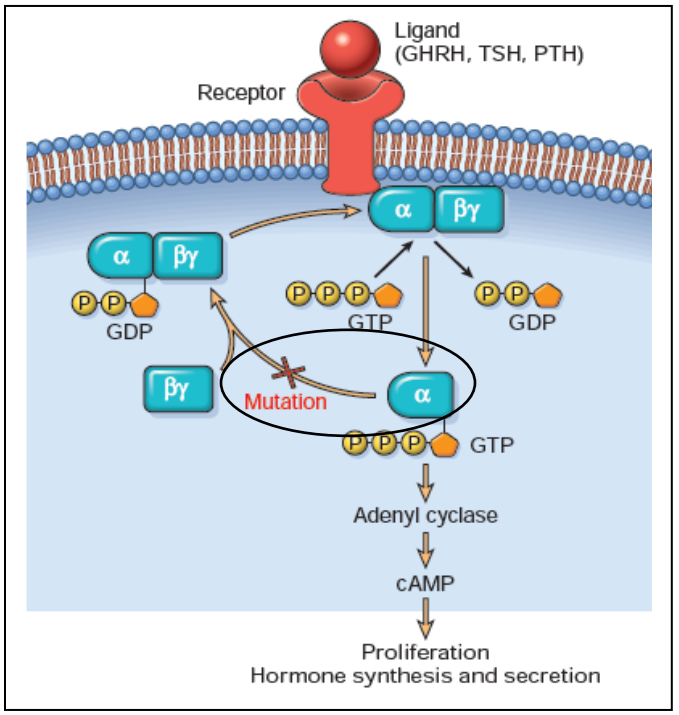
Remember that:

-Oncogene → gain of function mutation.

-Tumor suppressor gene→ loss of function mutation.

- **PRKAR1A** is a tumor suppressor gene might suffer from a germline mutation (loss of function) associated with familial tumor syndrome, these are associated with the autosomal dominant Carney complex.
- **Carney complex:**
  - Pituitary adenomas.
  - Myxoma (found in the heart and other tissues).
  - Hyperpigmentation of the skin.
- Germline mutation in MEN1→MEN1 Syndrome→ 3 Ps:
  - **P**ituitary adenomas.
  - **P**arathyroid tumors.
  - **P**ancreatic islet cell tumor (for example: insulinoma).
- Germline mutation in AIP→ Pituitary adenoma predisposition (PAP) syndrome.

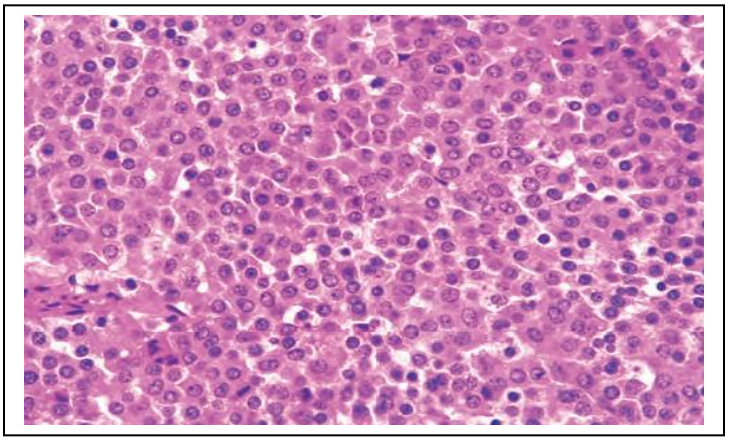
❖ GNAS mutation: (common in pituitary and thyroid adenomas)



- **In 40% of somatotroph adenomas and in the minority of corticotroph ones.**
- Not in Thyrotroph, lactotroph or gonadotroph adenomas.
- As long as the Alpha subunit is bound to the beta-gamma subunit it does not work. However, if it is not bound to the beta-gamma subunit it transmits the signal.
- If the alpha subunit is bound to GTP it means it is free from the beta-gamma subunit, but if the GTP is converted to GDP it means it is bound to the beta-gamma and is not working.
- GNAS mutation prevents the binding of GDP to the alpha subunit so only GTP is bound to it→ adenyl cyclase→ cAMP→ proliferation of the cell.
- The hypothalamus secretes GHRH which binds to the surface of the somatotroph in the anterior pituitary lobe, there we have a receptor (if there is a GNAS mutation then the alpha subunit will transmit the signal autonomously without the need for GHRH) →Proliferation of the cell→ somatotroph adenoma. (the same concept happens in the thyroid).

❖ Morphology of pituitary adenomas:

- Soft and well-circumscribed.
- In 30% of cases, they infiltrate neighboring tissues and on occasion the brain itself, these are called invasive adenomas (not cancer).
- Histologically: uniform/monophormic polygonal cells arrayed in sheets or cords, notice that there is less reticulin framework (supporting connective tissue) so it becomes soft and gelatinous.



- The presence of the reticulin network helps us differentiate between hyperplasia (which maintains the reticulin network) and between an adenoma (has less reticulin).

❖ Lactomorph adenoma:

- The most frequent/common type of hyperfunctioning pituitary adenoma, accounting for about 30% of all clinically recognized pituitary adenoma.
- Functional lactomorph adenoma is called a prolactinoma which causes prolactinemia→ (amenorrhea (absence of menstrual cycle), galactorrhea (milky discharge from the nipple unrelated to normal milk production in normal breast feeding), loss of libido and infertility), these obvious symptoms help in early diagnosis.
- Prolactin secretion by functioning adenomas is usually efficient (even microadenomas secrete sufficient amounts of prolactin to cause hyperprolactinemia)
- Diagnosis is easier in women (20-40 years) because of the unusual menstrual changes.
- Men might complain of loss of libido.
- Lactomorph adenoma underlies almost a quarter of cases of amenorrhea.
- In men and older women, the hormonal manifestations may be subtle, allowing the tumors to reach considerable sizes (Macroadenomas) before being detected clinically.
- Remember that prolactin level can also be elevated by nipple stimulation, as occurs during suckling in lactating women and as a response to many types of stress.
- Remember that prolactin is an acute phase reactant so it rises during inflammation.

❖ Some other pathologic causes of hyperprolactinemia:

- Loss of dopamine-mediated inhibition of prolactin secretion:
  - Damage of the dopaminergic neurons of the hypothalamus or damage of the pituitary stalk (e.g, due to head trauma), this leads to less input of dopamine going to the anterior pituitary →hyperprolactinemia.
  - Exposure to drugs that block dopamine receptors on lactotroph cells.
  - Any mass in the suprasellar compartment (e.g, a pituitary adenoma) may disturb the normal inhibitory influence of the hypothalamus on prolactin secretion, so a non-prolactin-producing pituitary adenoma may cause mild prolactinemia if large enough.
- Renal failure: the body can't get rid of prolactin →hyperprolactinemia.
- Hypothyroidism: Positive feedback due to hypothyroidism →Secretion of TRH →stimulation of lactotroph cells →hyperprolactinemia.

❖ Morphology of lactotroph adenoma:

- Sparsely granulated or densely granulated according to EM features of the cells.
- Lactotroph adenomas have a propensity to undergo dystrophic calcification, ranging from isolated psammoma bodies to extensive calcification of virtually the entire tumor mass ("pituitary stone")

❖ Treatment of lactotroph adenoma:

- Surgery.
- Bromocriptine (more commonly), a dopamine receptor agonist that causes the lesions to diminish in size