Pituitary gland Pathology
Lecture 2

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Pituitary adenoma

- **Monomorphic**: one cell type. All cells look similar, whereas in the normal pituitary several cell types exist.

This figure represents a normal pituitary gland tissue (as we said it composed of 3 cell types ... chromophobes, acidophils, basophils...)

This is a section from a pituitary adenoma which shows that the cells are monomorphic (similar to each other).
Normal pituitary.. Several cell types

In normal pituitary you can't see monomorphic cells.
Adenoma.. One cell type = monomorphic appearance (similar in shape and size)

The cells of pituitary adenoma are cuboidal having moderate amount of cytoplasm and inconspicuous small nucleoli, also have fine chromatin as any endocrine tumor.
Notes

- Cellular **monomorphism** and the **absence of a significant reticulin network** distinguish pituitary adenomas from non-neoplastic anterior pituitary parenchyma (as the normal anterior pituitary gland cells have reticulin fibers network surrounding each cell)

- The functional status of the adenoma cannot be reliably predicted from its histologic appearance. *(We depend on the serum level of the hormones)*

- Adenomas that have **TP53 mutations** demonstrate brisk mitotic activity and are called **atypical adenomas** to reinforce their potential for **aggressive behavior**.
Atypical adenoma with increased mitosis. These have TP53 mutation and are aggressive.

If the adenoma has TP53 mutation plus mitotic figures we call it atypical adenoma which is very aggressive.
1. Prolactinomas

These are adenomas that produce prolactin. = hyperprolactinemia

Hyperprolactinemia causes:

1. Amenorrhea (loss of menses in females) and galactorrhea (production of milk in males and non-lactating women)
2. Loss of libido, and infertility.

Prolactinomas usually are diagnosed at an earlier stage in women of reproductive age than in other persons.. Because they are more likely to have obvious symptoms (female with amenorrhea will do investigations to know the cause, one of the investigations is the measurement of serum prolactin levels, if high >> the cause of amenorrhea is prolactinoma)
Other causes of hyperprolactinemia,

a. **Pregnancy** *(physiological cause)*, and **high-dose estrogen therapy**, 

b. **Dopamine-inhibiting drugs** *(e.g., reserpine).* *(because dopamine normally inhibits prolactin secretion from anterior pituitary so any drug inhibits dopamine will cause hyperprolactinemia )

c. Any **mass in the suprasellar compartment** may disturb the normal inhibitory influence of hypothalamus on prolactin secretion, resulting in hyperprolactinemia-a mechanism known as the **stalk effect**.
2. Growth Hormone-Producing (Somatotroph) Adenomas

- Are the **second most common** type of functioning pituitary adenoma.
- May be quite large at time of diagnosis because the clinical manifestations of excessive growth hormone may be subtle **or minimal**.
clinical manifestations of GH producing adenomas:

- Increased growth hormone (production and secretion) can cause **Gigantism** or **acromegaly**.

  - If a growth hormone-secreting adenoma occurs before the epiphyses closes (in children) it causes **gigantism**.

**gigantism**: generalized increase in body size, with disproportionately long arms and legs.
gigantism

As you can see the patient has generalized increase in the body size with long arms and legs.
acromegaly

- If elevated levels of growth hormone (or somatotroph cells adenomas) persist, or develop after closure of the epiphyses (After puberty), affected persons develop **acromegaly**, in which:

1. **Growth** is most conspicuous in soft tissues, skin, and viscera and in the bones of the face, hands, and feet.

2. **Enlargement of the jaw** results in its protrusion with separation of the teeth.

1. **Enlarged hands and feet** with broad, sausage-like fingers.
3. Corticotroph cell adenomas

Are ACTH producing pituitary adenomas

May be:

1. Clinically silent OR

2. May cause hypercortisolism = increased cortisol, manifested clinically as Cushing syndrome (the most common cause of Cushing syndrome)

✓ We know that ACTH stimulates the adrenal gland to produce cortisol and this cortisol has inhibitory effect on ACTH secretion

✓ One mode of therapy for Cushing syndrome is surgical excision of the adrenal gland which will lead to loss of the feedback inhibition of cortisol on ACTH secretion, and this will lead to rapid enlargement and more aggressive behavior of ACTH producing adenoma (Nelson syndrome).

• Large, clinically aggressive corticotroph cell adenomas may develop after surgical removal of the adrenal glands for treatment of Cushing syndrome, this condition is Nelson syndrome.
• The reason is the metabolic demands and the loss of the feedback mechanism.

➢ Because ACTH is synthesized as part of a larger pro-hormone substance that includes melanocyte-stimulating hormone (MSH) could be used as a diagnostic measure, hyperpigmentation may be a feature.
4. Gonadotroph LH-producing and FSH adenomas

- Can be difficult to recognize, because they secrete hormones inefficiently, and the secretory products usually do not cause a recognizable clinical syndrome.
Pituitary carcinomas

- are exceedingly rare and in addition to local extension beyond the sella turcica, these tumors virtually always demonstrate distant metastases.

Generally: Most endocrine carcinomas are diagnosed depending on behavior (presence of metastases) and not on histological appearance. i.e under the microscope adenoma and carcinoma can look similar. You need to know the clinical information (provided by the treating physician) and check if the patient has metastatic disease in order to call the lesion carcinoma.
Hyperpituitarism
(over production of pituitary hormones)

• MOST COMMON CAUSE: functional adenoma.

• Other causes:
  1. Hyperplasia (the increase in no. of pituitary cells)
  2. Carcinoma (rare)
  3. Secretion of pituitary hormones by nonpituitary tumors. (For example, there is increase in ACTH secretion by non-pituitary tumors such as lung small cell carcinoma (ectopic production))
  4. Hypothalamic disorders.
Hypopituitarism
(decrease production of hormones from the anterior pituitary)

• Occurs if there is Loss of at least 75% of anterior pituitary

• Causes:
  a. Congenital absence (exceedingly rare).
  b. Hypothalamic tumors, associated with posterior pituitary dysfunction.
  c. Nonfunctioning pituitary adenomas. Most common/occurs when the adenoma compresses normal pituitary tissue and affects its function. (Non-secreting, so don’t produce any clinical manifestations because there are no hormones, by becoming enlarged these tumors might compress the normal pituitary gland causing decreased production of the hormones (hypopituitarism))
d. Ischemic necrosis of the anterior pituitary, e.g. Sheehan syndrome (postpartum period)

e. Ablation of the pituitary by surgery or irradiation (radiation therapy as a part of treatment for head and neck tumors causes fibrosis of the anterior pituitary gland and decreases the production of hormones)

f. Inflammatory lesions (of hypothalamus and pituitary) such as sarcoidosis (is characterized by the presence of non-caseating granulomas that might destruct the parenchyma of hypothalamus and pituitary gland) or tuberculosis (is characterized by the presence of caseating granulomas which might destruct the anterior pituitary gland)

g. Trauma and Metastatic neoplasms involving the pituitary (the most common metastatic tumors are malignant tumors of the lung and breast)
Sheehan syndrome

• Or postpartum necrosis of anterior pituitary, is the most common form of clinically significant ischemic necrosis of the anterior pituitary.

• During pregnancy, the anterior pituitary enlarges considerably, because of an increase in the size and number of prolactin-secreting cells and this physiologic enlargement is not accompanied by an increase in blood supply from the low-pressure portal venous system.

• The enlarged gland is thus vulnerable to ischemic injury, especially in women who experience significant hemorrhage and hypotension during the postpartum period.

• Note: Sheehan syndrome is named after a British pathologist who described the condition.
POSTERIOR PITUITARY SYNDROMES.

There are two hormones which are produced by the hypothalamus and stored in the posterior pituitary (oxytocin and ADH).

- Impairment of oxytocin synthesis and release has not been associated with significant clinical abnormalities.

Oxytocin has physiologic action, is stimulates contraction of the uterine muscles aiding in labor, also it is associated with the stimulation of the muscles surrounding the lactiferous duct of the breast aiding in lactation.

- The clinically important posterior pituitary syndromes involve ADH = vasopressin.

We have to syndromes related to ADH abnormalities:
1) ADH deficiency which leads to DI
2) Syndrome of inappropriate ADH secretion which caused by increased production of ADH.
ADH deficiency

- causes **diabetes insipidus (DI)** characterized by **excessive urination (polyuria)** caused by an inability of the kidney to properly resorb water from the urine
- **SO:** patients are thirsty and have **polydipsia** = excessive drinking

- The Doctor also mentioned another syndrome related to ADH which is **(syndrome of inappropriate antidiuretic hormone secretion (SIADH))** which is caused by excessive secretion of ADH.
Diabetes insipidus can result from several causes,

a. **Head trauma, Neoplasms.**

b. **Inflammatory disorders** (such as sarcoidosis and tuberculosis) and **surgical procedures** of the hypothalamus and pituitary.

c. The condition may be **idiopathic**.

**Note:** Diabetes insipidus from ADH deficiency is designated as **central DI**, to differentiate it from **nephrogenic DI**.
• The clinical manifestations of DI include:

a. The excretion of large volumes of dilute urine with an inappropriately low specific gravity

b. Serum sodium and osmolality are increased as a result of excessive renal loss of free water resulting in thirst and polydipsia

• Patients who can drink water generally can compensate for urinary losses; patients who are bedridden or are limited in their ability to obtain water may develop life threatening dehydration.