by: Marah Marahleh

lec: Pathology of adrenal gland

**note : the sheet contain many info from the book as the doctor hurried in her lecture .

good luck and sorry for any mistakes...
Pathology of adrenal gland

**Slides in bold and book in red**

- adrenal glands: cortex
  - medulla

**Diseases of the adrenal cortex** can be conveniently divided into those associated with cortical hyperfunction and those characterized by cortical hypofunction.

1. **ADRENOCORTICAL HYPERFUNCTION (HYPERADRENALISM)**
   1. Cushing syndrome
   2. hyperaldosteronism
   3. adrenogenital or virilizing syndromes

**Hypercortisolism and Cushing Syndrome**

- Elevation in glucocorticoid levels
- ACTH-dependent Cushing syndrome
- ACTH-independent Cushing syndrome

**Causes of Hypercortisolism, typically manifested as Cushing syndrome:**

- Exogenous/iatrogenic ------- MC
- iatrogenic: administration of exogenous glucocorticoids

- Endogenous:

  *hypothalamic-pituitary diseases:*

1. hypersecretion of ACTH by pituitary adenoma-**Cushing disease**--70% ----MC
   The prevalence of this disorder is about four times higher among women than among men, and it occurs most frequently during young adulthood (the 20s and 30s)

2. corticotroph cell hyperplasia
   Corticotroph cell hyperplasia may be primary or, much less commonly, secondary to excessive ACTH release by a hypothalamic corticotropin-releasing hormone (CRH)–producing tumor
3- Corticotropin-releasing hormone (CRH)–producing tumor – tumors in the hypothalamus

* non-pituitary neoplasms, 10% --- ectopic ACTH, ectopic CRH

The most common neoplasm causing cushing syndrome is small cell carcinoma of the lung, other neoplasms, include carcinoids, medullary carcinomas of the thyroid, and PanNETs (Pancreatic neuroendocrine tumors) they mainly produce ACTH but could produce CRH though it is less common.

*Primary adrenal neoplasms, such as adrenal adenoma and carcinoma, and rarely, primary cortical hyperplasia, are responsible for about 15% to 20% of cases of endogenous Cushing syndrome. This form of Cushing syndrome is also designated ACTH-independent Cushing syndrome, or adrenal Cushing syndrome, because the adrenals function autonomously.

- adrenocortical neoplasms
  - adenoma—15-20%
  - Carcinoma –less common

- Primary cortical hyperplasia → hyperplasia in adrenal cortex (usually nodular)
- Secondary cortical hyperplasia → ACTH production from pituitary diseases (diffuse)

Figure 19.13 Schematic representation of the various forms of Cushing syndrome: The three endogenous forms, as well as the more common exogenous (iatrogenic) form. ACTH, adrenocorticotropic hormone.
**Morphology**

* The main lesions of Cushing syndrome are found in the pituitary and adrenal glands

1- The pituitary in Cushing syndrome:

Crooke hyaline change ???

--Change in pituitary gland in cushing syndrome :

All cases of hypercortisolism regardless of the cause : the pituitary contain **crooke hyaline change**

→ which is a change in ACTH producing cells in the pituitary ; on microscope : the normal basophilic granular cytoplasm of corticotropes change to homogenous basophilic cytoplasm due to the accumulation of intermediate keratin .

--we see this change in all patient of cushing syndrome (cushing disease/ exogenous /endogenous) .

2- adrenal glands in Cushing syndrome:

1) **Cortical atrophy**
   Most common cause is exogenous cortisol , other cause include neoplasm (adenoma/carcinoma) which gives cortisol & through feedback inhibition of corticotropes in pituitary cause atrophy of normal cortex adjacent to the neoplasm.

2) **diffuse hyperplasia** → in ACTH producing tumors → pituitary adenoma/carcinoma → hypothalamic tumors → ectopic production of ACTH (small cell carcinoma of the lung /carcinoids/ medullary carcinomas of the thyroid)

3) **macronodular or micronodular hyperplasia:**
   in primary adrenal hyperplasia which is either macronodular (nodule >3cm) or micronodular ( <3mm)

4) an adenoma

5) carcinoma
- Bilateral cortical atrophy:

- Exogenous glucocorticoids

In patients in whom the syndrome results from exogenous glucocorticoids, suppression of endogenous ACTH results in bilateral cortical atrophy, due to a lack of stimulation of the zona fasciculata and zona reticularis by ACTH.

- The zona glomerulosa is of normal thickness in such cases because mineralocorticoids (aldosterone) is controlled by Renin-angiotensin system.

-Diffuse hyperplasia:

  - ACTH-dependent Cushing syndrome

  - Both glands are enlarged (each 30 g) normal = 4-5 g

-Macronodular or micronodular hyperplasia:

  - Primary cortical hyperplasia

    - Macronodules: 3 cm or greater

    - Micronodules: 1 to 3 mm pigmented nodules (lipofuscin)

• Functional adenomas or carcinomas of the adrenal cortex:

  - Adenomas: yellow, capsules, less than 30 g → The yellow color derives from presence of lipid-rich cells that produce steroids.

  - Carcinomas: nonencapsulated, 200 to 300 g or capsulated with interruption of the capsule.

  - The adjacent adrenal cortex and that of the contralateral adrenal gland are atrophic as a result of suppression of endogenous ACTH by high cortisol levels.

• Clinical Features: Cushing syndrome:

  - Hypertension and weight gain → early manifestations

  - Truncal obesity, moon facies, buffalo hump → later manifestations because of the characteristic centripetal distribution of adipose tissue

  - Decreased muscle mass and proximal limb weakness → selective atrophy of fast-twitch (type II) myofibers,

  - Hyperglycemia, glucosuria, and polydipsia → Because glucocorticoids induce gluconeogenesis and inhibit the uptake of glucose by cells
- **cutaneous striae (loss of collagen/ catabolic)** The catabolic effects on proteins cause loss of collagen and resorption of bone

- **Osteoporosis (resorption of bone/ catabolic)**

- **Infections (suppress the immune response)**

- **Hirsutism**

- **menstrual abnormalities**

- **mental disturbances (mood swings, depression, and frank psychosis)**

- **Skin pigmentation:** Extraadrenal Cushing syndrome caused by pituitary or ectopic ACTH secretion secondary to melanocyte-stimulating activity in the ACTH precursor molecule → not in all cases

---

**Hyperaldosteronism**

Hyperaldosteronism is the generic term for a group of closely related conditions characterized by chronic excess aldosterone secretion.

Either

- Primary due to adrenal hyperplasia or carcinoma OR
- Secondary due to activation of rennin angiotensin system.

*not associated with pituitary diseases because aldosterone is controlled by rennin angiotensin system.*

- **Secondary hyperaldosteronism:**

  - activation of the renin-angiotensin system

  - increased levels of plasma renin

**Causes:**

- Decreased renal perfusion (renal artery stenosis)
- Pregnancy (estrogen)
- Arterial hypovolemia + edema (congestive heart failure, cirrhosis, nephrotic syndrome)

*Figure 19-38: A patient with Cushing syndrome. Characteristic features include central obesity, “moon facies,” and abdominal stria.*
Quick review of rennin angiotensin system:

- Low BP → low perfusion to the kidneys → activation of rennin secretion from juxtaglomerular kidney cells → rennin convert angiotensinogen to angiotensin I in plasma → angiotensin I is converted to angiotensin II in the lung → angiotensin II stimulate zona glomerulosa to secrete aldosterone.

Soo .. anything that decrease renal perfusion leads to activation of rennin secretion and that include: 1-hypovolemia: shock /hemorrhage /septicemia.

3- intrinsic cause in kidney like renal stenosis

- **Primary hyperaldosteronism:**
  - suppression of the renin-angiotensin system
  - decreased plasma renin activity
  
  **Causes:**
  - bilateral nodular hyperplasia of the adrenal glands (60%) → MC
  - Adrenocortical adenoma (35%) → Conn syndrome
  Conn syndrome: solitary aldosterone-secreting adenoma
  - Adrenocortical carcinoma
  - familial hyperaldosteronism (aldosterone synthase gene, CYP11B2) genetic defect that leads to overactivity of the aldosterone synthase gene, CYP11B2.

- **Aldosterone-producing adenomas:**
  - solitary,
  - small (less than 2 cm in diameter)
  - well-circumscribed
  - bright yellow
  And are composed of lipid-laden cortical cells more closely resembling fasciculata cells than glomerulosa cells (the normal source of aldosterone)

  **Spironolactone bodies** ???? eosinophilic, laminated cytoplasmic inclusions
  These typically are found after treatment with the antihypertensive agent spironolactone, which is the drug of choice in primary hyperaldosteronism.

  the adjacent adrenal cortex and that of the contralateral gland are ???? normal, because ACTH levels are normal cuz aldosterone is controlled by rennin angiotensin system.

- **Clinical Features:**
Hypertension

Primary hyperaldosteronism may be the most common cause of secondary hypertension which is treatable upon the removal of the cause (adenoma).

Hypokalemia ➔ neuromuscular manifestations (weakness, paresthesias, visual disturbances, and tetany) from renal potassium wasting

- **Treatment:**
  - Surgical excision ➔ for neoplasm
  - Aldosterone antagonist ➔ patients with primary hyperaldosteronism due to bilateral hyperplasia, which often occurs in children and young adults.
  - The treatment of secondary hyperaldosteronism rests on correcting the underlying cause of the renin-angiotensin system hyperstimulation.

**Adrenogenital Syndromes**

Excess of androgens may be caused by a number of diseases, including primary gonadal disorders and several primary adrenal disorders.

- **Androgen excess —— virilization**

Virilization is a condition in which women develop male-pattern hair growth and other masculine physical traits like Hirsutism/deepening of the voice/muscle build.

The adrenal causes of androgen excess include:

- Adrenocortical neoplasms —— Carcinoma are more likely to be carcinomas than adenomas unlike the other conditions discussed previously.
- Congenital adrenal hyperplasia

- Could be isolated syndrome or in combination with features of Cushing disease —— ACTH

If the cause is ACTH producing tumors then it will be in combination of features of cushing syndrome (virilization+hypercortisolism) or if the cause is cortical adenoma/carcinoma (mainly) then it is presented as isolated syndrome.
**congenital adrenal hyperplasia (CAH): autosomal recessive** two alleles of the gene must be affected.

- Enzyme defect ---- adrenal steroid biosynthesis (cortisol)

The adrenal cortex secretes two compounds—dehydroepiandrosterone and androstenedione—which require conversion to testosterone in peripheral tissues for their androgenic effects.

In these conditions, decreased cortisol production results in a compensatory increase in ACTH secretion due to absence of feedback inhibition. The resultant adrenal hyperplasia causes increased production of cortisol precursor steroids, which are then channeled into synthesis of androgens with virilizing activity.

- increase in ACTH
- Adrenal hyperplasia
- androgens with virilizing activity

- Certain enzyme defects also may impair aldosterone secretion, adding salt loss to the virilizing syndrome could lead to dehydration which is especially dangerous in infants.

The most common enzymatic defect is in:

- **21-hydroxylase deficiency (CYP21A2 gene)** which accounts for more than 90% of cases.
- **11β-hydroxylase deficiency**

**MORPHOLOGY**

the adrenals are hyperplastic bilaterally (expanding to 10 to 15 times their normal weights) due to ACTH affect & are • Brown as a result of depletion of all lipid /The proliferating cells mostly are compact, eosinophilic, lipid-depleted cells, intermixed with lipid-laden clear cells

- adrenomedullary dysplasia has been reported in patients with the salt-losing 21-hydroxylase deficiency. This is characterized by incomplete migration of the chromaffin cells to the center of the gland, with pronounced intermingling of nests of chromaffin and cortical cells in the periphery.

- Hyperplasia of corticotroph (ACTH-producing) cells is present in the anterior pituitary due to feedback from the adrenals.

**Clinical Features:**
Depending on the nature and severity of the enzymatic defect, the onset of clinical symptoms may occur in:

→ perinatal period,
→ later childhood,
→ Adulthood

**All have excessive androgenic activity + additional features according to the enzymatic defect.**

- Females: masculinization (virilization)
  - clitoral hypertrophy and pseudohermaphroditism in infants
  - delayed menarche (delayed puberty)
  - oligomenorrhea

- In males:
  - enlargement of the external genitalia
  - and other evidence of precocious puberty in prepubertal patients
  - oligospermia in older patients

- hirsutism, and acne in postpubertal girls.

**pseudohermaphroditism:**
→ refers to an individual with ovaries but with secondary sexual characteristics or external genitalia resembling those of a male (from the net)

→ A female with genotype of XX and internal genital organs of female but the phenotype of a male (from doctor)

- Other features include:
  - sodium retention and hypertension
  - 11β-hydroxylase deficiency, the accumulated intermediary steroids have mineralocorticoid activity.
  - Salt (sodium) wasting

21-hydroxylase deficiency, the enzymatic defect is severe enough to produce mineralocorticoid deficiency.

- Neonate:

  Ambiguous genitalia → infant's external genitals don't appear to be clearly either male or female. In a baby with ambiguous genitalia, the genitals may not be well-formed or the baby
may have characteristics of both sexes. The external sex organs may not match the internal sex organs or genetic sex.

vomiting,

dehydration, and salt wasting.

Treatment of CAH: exogenous glucocorticoids

ADRENOCORTICAL NEOPLASMS

• Hyperadrenalism
• functional adenomas: hyperaldosteronism, Cushing syndrome
• Carcinoma: virilization, rare
• Non-functional

ADRENAL INSUFFICIENCY

The patterns of adrenocortical insufficiency can be divided into three general categories

(1) primary acute adrenocortical insufficiency (adrenal crisis);
(2) primary chronic adrenocortical insufficiency (Addison disease);
(3) secondary adrenocortical insufficiency.

Acute Adrenocortical Insufficiency

*Causes :

• chronic adrenocortical insufficiency--- acute crisis---- after any stress

Persons with chronic adrenocortical insufficiency may develop an acute crisis after any stress that taxes their limited physiologic reserves

• patients maintained on exogenous corticosteroids: rapid withdrawal of steroids failure to increase steroid doses---- stress , because of the inability of the atrophic adrenals to produce glucocorticoid hormones.

• Massive adrenal hemorrhage: may destroy enough of the adrenal cortex to cause acute adrenocortical insufficiency may occur in Anticoagulant therapy, DIC(Disseminated intravascular coagulation) , pregnancy, overwhelming sepsis (Waterhouse-Friderichsen Syndrome)
• Waterhouse-Friderichen syndrome:

Mainly by *Neisseria meningitidis* septicemia—endotoxin---

DIC (*The pathogenesis of the Waterhouse-Friderichen syndrome remains unclear but probably involves endotoxin-induced vascular injury with associated disseminated intravascular coagulation*)

Other organisms include: *Pseudomonas spp.*, *pneumococci*, *Haemophilus influenzae*

**Chronic Adrenocortical Insufficiency:**

• **Addison Disease:** resulting from progressive destruction of the adrenal cortex

**Causes:**

More than 90% of all cases are attributable to one of four disorders:

1 - **autoimmune adrenalitis** → 60% to 70% of cases

2- **infections:** tuberculosis, fungi (*Histoplasma capsulatum* and *Coccidioides immitis*)

3 - **the acquired immune deficiency syndrome (AIDS):** AIDS patients are more prone to infections (*cytomegalovirus*, *Mycobacterium avium-intracellulare*), and infiltrating tumors like kaposi sarcoma

4- **metastatic cancer:** lung and breast carcinomas most commonly although many other neoplasms, including gastrointestinal carcinomas, malignant melanomas, and hematopoietic neoplasms, also may metastasize to the organ

Others:

- Amyloidosis
- Sarcoidosis
- Hemochromatosis

• **Autoimmune adrenalitis:** - Mc

- **two autoimmune polyendocrine syndromes (APS):**

**APS1:** caused by mutations in the autoimmune regulator (AIRE) gene on chromosome 21
chronic mucocutaneous candidiasis and abnormalities of skin, dental enamel, and nails (ectodermal dystrophy), organ-specific autoimmune disorders (autoimmune adrenalitis, autoimmune hypoparathyroidism, idiopathic hypogonadism, pernicious anemia)

APS2: manifests in early adulthood

adrenal insufficiency and autoimmune thyroiditis or type 1 diabetes

Adrenal: lymphoid infiltrate → histology

Secondary Adrenocortical Insufficiency

• hypothalamus and pituitary disorders

• low serum ACTH

• prompt rise in plasma cortisol levels in response to ACTH administration

In patients with primary disease, serum ACTH levels may be normal, but the destruction of the adrenal cortex does not permit a response to exogenously administered ACTH in the form of increased plasma levels of cortisol. By contrast, secondary adrenocortical insufficiency is characterized by low serum ACTH and a prompt rise in plasma cortisol levels in response to ACTH administration.

• no hyperpigmentation (With secondary disease, the hyperpigmentation of primary Addison disease is lacking because melanotropic hormone levels are low)

Morphology:

• Adrenal: Atrophic cortex, intact medulla

• Clinical Features of adrenocortical insufficiency: do not appear until at least 90% of the adrenal cortex has been compromised

- progressive weakness and easy fatigability

- Gastrointestinal disturbances (anorexia, nausea, vomiting, weight loss, and diarrhea)

- hyperpigmentation of the skin and mucosal surfaces: primary adrenal disease → face, axillae, nipples, areolae, and perineum are particularly common sites of hyperpigmentation

- hyperkalemia, hyponatremia, volume depletion, and hypotension: primary adrenal disease

- Hypoglycemia

- acute adrenal crisis: stress--- intractable vomiting, abdominal pain, hypotension, coma, and vascular collapse. Death follows rapidly unless corticosteroids are replaced immediately

ADRENAL MEDULLA
- **Pheochromocytoma**: are neoplasms composed of chromaffin cells that synthesize and release catecholamines

  **rule of 10s:**

  10% extraadrenal--------called **paragangliomas**

  Paraganglia is different from chromaffin cells in that it has two types

  → sympathetic: in Zuckerkandl and secrete catecholamine  → parasympathetic: in carotid bodies and are chemoreceptor.

  10% bilateral, but rise to 50% in familial cases

  10% malignant

  10% no hypertension (paroxysmal)

  **25% familial germline mutation in one of 6 genes**: RET (causes type 2 MEN syndromes), NF1, VHL (von Hippel-Lindau disease), SDHB, SDHC, SDHD (the succinate dehydrogenase complex)

  **Morphology**

  ![](image)

  The nuclei of the neoplastic cells are often quite pleomorphic. Both capsular and vascular invasion may be encountered in benign lesions, and the mere presence of mitotic figures does not imply malignancy.

  the definitive diagnosis of malignancy in pheochromocytomas is based exclusively on the presence of metastases

- **Clinical Features:**
- Hypertension (abrupt, sustained (2/3 of patients) or episodic) → The predominant clinical manifestation mainly episodic occurs in fewer than half of patients.

- Tachycardia, palpitations, headache, sweating, tremor, and a sense of apprehension

- Sudden cardiac death (arrhythmias) secondary to catecholamine-induced myocardial irritability and ventricular arrhythmias

- Secrete ACTH and somatostatin → may therefore be associated with clinical features related to the effects of these

- The laboratory diagnosis of pheochromocytoma is based on demonstration of increased urinary excretion of free catecholamines and their metabolites, such as vanillylmandelic acid and metanephrines.

- Isolated benign pheochromocytomas are treated with surgical excision.

- With multifocal lesions, long-term medical treatment for hypertension may be required.

**MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES**

*group of inherited diseases resulting in proliferative lesions (hyperplasias, adenomas, and carcinomas) of multiple endocrine organs*

*distinctive features:

- Inherited
- Younger age
  - Multifocal organs either synchronously or metachronously.
- Multifocal
- Asymptomatic stage of endocrine hyperplasia
- More aggressive

Multiple Endocrine Neoplasia Type 1

- AD (autosomal dominant)
• **MEN1 gene (tumor suppressor), ch 11**→ inactivation of both alleles of the gene is believed to be the basis for tumorigenesis

• **3 Ps:**
  - Parathyroid (hyperplasia, adenomas) → 80-95%
  - Pancreas (gastrinomas, insulinomas) → Endocrine tumors of the pancreas are the leading cause of death in MEN-1

the gastrinomas arising in MEN-1 syndrome are far more likely to be located within the duodenum than in the pancreas.

• Pituitary (prolactin adenoma → most frequent)

**Multiple Endocrine Neoplasia Type 2**

• **AD**

• **RET (proto-oncogene), ch 10**→ activating mutations

• **MEN type 2A:**

  **Thyroid:** Medullary carcinoma → in virtually all untreated cases

  **Adrenal medulla:** pheochromocytomas → in 50% of the patients but only 10% of these tumors are malignant.

  **Parathyroid:** parathyroid gland hyperplasia (10% to 20%)

• **Multiple Endocrine Neoplasia Type 2B:** RET mutation involving a single–amino acid change

  **Thyroid (as 2A)**

  **Adrenal medulla (as 2A)**

  Extraendocrine manifestations:

  - ganglioneuromas of mucosal sites (gastrointestinal tract, lips, tongue)
  - marfanoid habitus → in which overly long bones of the axial skeleton give an appearance resembling that in Marfan syndrome

  all persons carrying germline RET mutations are advised to have prophylactic thyroidectomy to prevent the inevitable development of medullary carcinomas