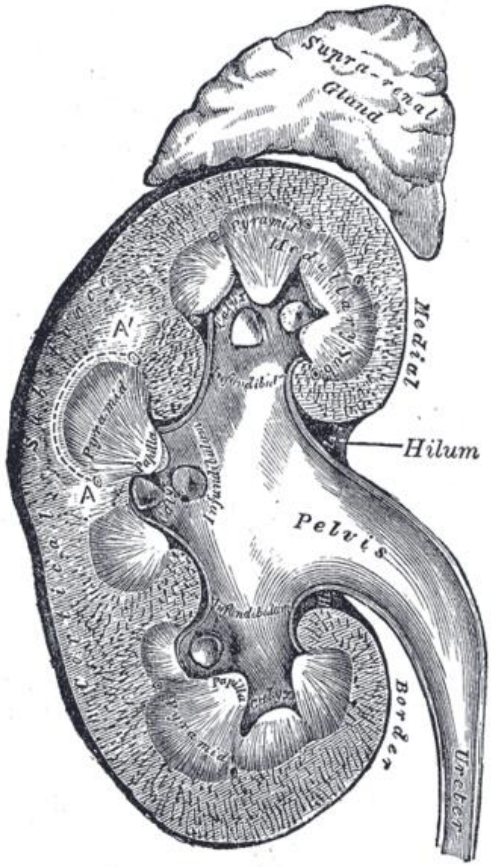
Lecture 3
Adrenal Gland

{ ومن لم يذق مرّ التعلُّمِ ساعةً.. تجرع ذلّ الجهل طوال حياتهِ }

Revised by
هشام الغفيلي & خولة العماري

Red: Important. Grey: Extra Notes Doctors Notes will be in text boxes



Objectives:

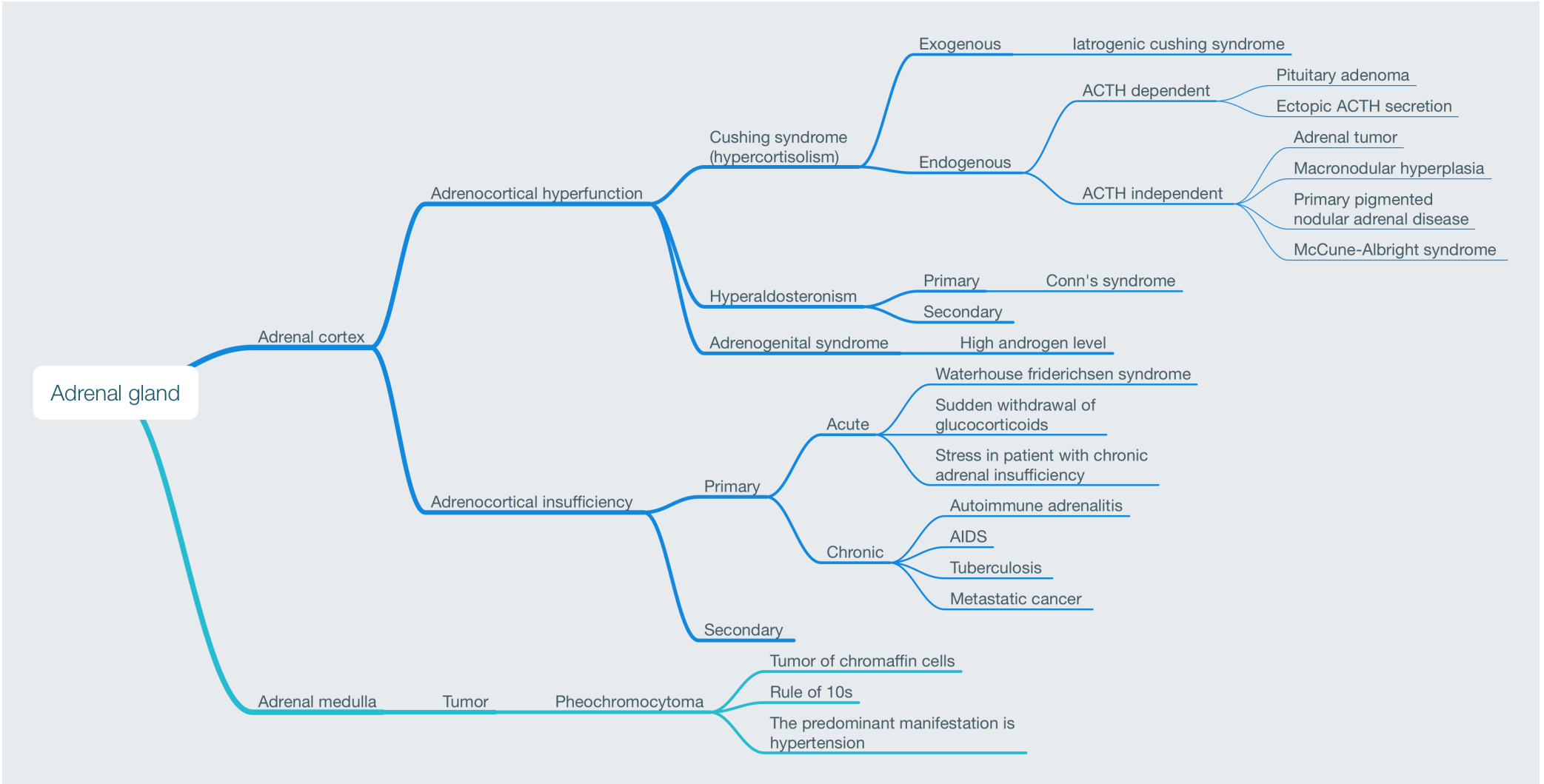
- Understand the structure and its function of the adrenal glands
- Know the common disorders that can affect the adrenal medulla
- Know the disorders that can cause hypo or hyperfunction of adrenal cortex.

The student should:

- Recognize the variants of hyperadrenalism
- Recognize the variants of hypoadrenalism
- Understand the histopathological features and molecular pathology of both medullary (pheochromocytoma) and adrenocortical neoplasms.

References: Lecture Slides, Robbins, Dr. Rikabbi & Dr. Hala's Notes.

** The lecture is only 6.5 pages; the rest are extra information & MCQs**


Adrenal gland
Adrenal cortex
Adrenocortical hyperfunction
Cushing syndrome (hypercortisolism)
Exogenous
Iatrogenic cushing syndrome
Endogenous
ACTH dependent
Pituitary adenoma
Ectopic ACTH secretion
ACTH independent
Adrenal tumor
Macronodular hyperplasia
Primary pigmented nodular adrenal disease
McCune-Albright syndrome
Hyperaldosteronism
Primary
Conn's syndrome
Secondary
Adrenogenital syndrome
High androgen level
Adrenocortical insufficiency
Primary
Acute
Waterhouse friderichsen syndrome
Sudden withdrawal of glucocorticoids
Stress in patient with chronic adrenal insufficiency
Chronic
Autoimmune adrenalitis
AIDS
Tuberculosis
Metastatic cancer
Secondary
Adrenal medulla
Tumor
Pheochromocytoma
Tumor of chromaffin cells
Rule of 10s
The predominant manifestation is hypertension

The adrenal cortex synthesizes three different types of steroids:

- ***Mineralocorticoids,*** the most important being aldosterone, which are generated in the **zona glomerulosa**.
- ***Glucocorticoids*** (principally cortisol), which are synthesized primarily in the **zona fasciculata**, with a small contribution from the zona reticularis
- ***Sex steroids*** (estrogens and androgens), which are produced largely in the **zona reticularis**.

Adrenocortical Hyperfunction:

There are three distinctive hyperadrenal clinical syndromes, each caused by abnormal production of one or more of the hormones produced by the three layers of the cortex:

(1) ***Cushing syndrome***, characterized by an excess of **cortisol**.
(2) ***Hyperaldosteronism.***
(3) *Adrenogenital* or *virilizing syndromes* caused by an excess of androgens.

Hyperaldosteronism (we call it Conn's only when it's due to adrenal adenoma)

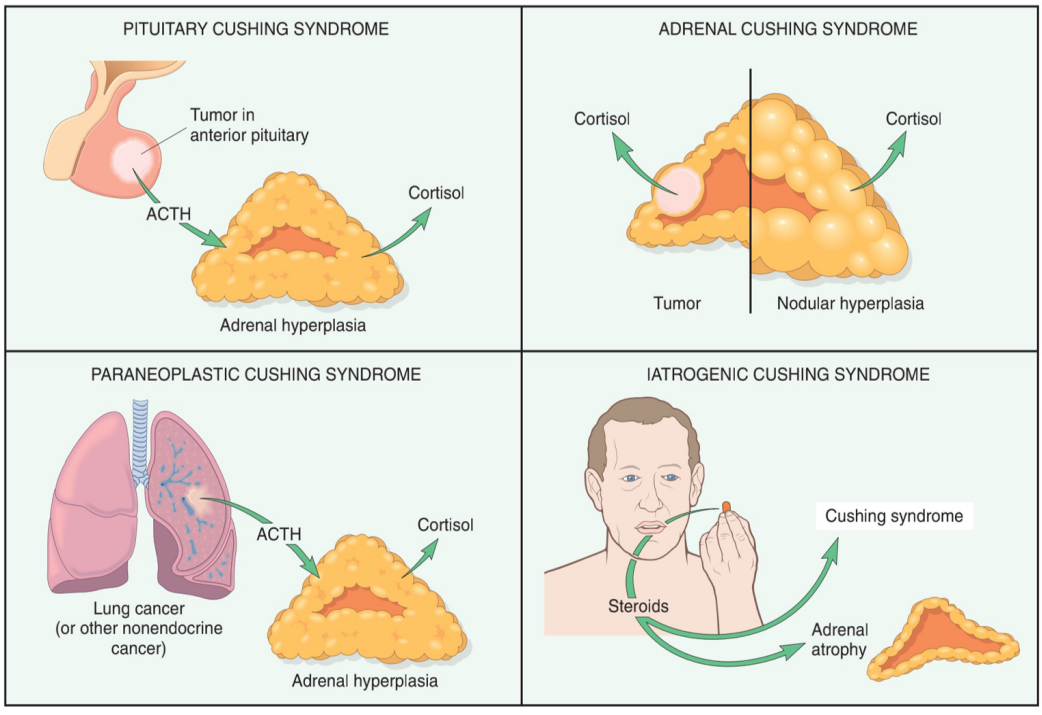
Hypercortisolism "Cushing Syndrome":

Hypercortisolism, typically manifested as Cushing syndrome, is caused by any condition that produces an elevation in glucocorticoid levels

It could be:

- **Exogenous**[1]:
  Most common cause of Cushing syndrome is the *administration of exogenous glucocorticoids* ("iatrogenic" Cushing syndrome)
- **Endogenous:**
  The endogenous causes can, in turn, be divided into those that are ACTH dependent (cortisol needs ACTH to be secreted) and those that are ACTH independent (cortisol is secreted without ACTH stimulation).

Iatrogenic (means due to treatment in general, it could be surgery or medication). For treatment of rheumatoid arthritis or most of the autoimmune diseases.



[1] ياخذون ستيرويدز للعلاج

Causes of endogenous Hypercortisolism	(%)[2]	(F:M)[3]
ACTH-DEPENDENT		
Cushing disease (ACTH-producing microadenoma; rarely CRH-dependent pituitary hyperplasia) (common in young adults 20s-30s) (associated with bilateral nodular cortical hyperplasia).	70	4:1
Ectopic corticotropin syndrome (ACTH-secreting pulmonary small-cell carcinoma, bronchial carcinoid tumor) (if removed, person will return to normal)	10	1:1
ACTH-INDEPENDENT (adrenal Cushing syndrome)		
Adrenal adenoma (**unilateral adrenocortical neoplasm**) → contralateral adrenal atrophy.	10-15	F > M
Adrenal carcinoma (unilateral adrenocortical neoplasm) → **contralateral adrenal atrophy.**	5	F > M
Primary cortical hyperplasia (**rare**) → macro- or micronodular hyperplasia with pigmented nodules (lipofuscin).	< 2	1:1

Ectopic ACTH syndrome: there are tumors in the body, especially small cell carcinoma, carcinoid tumor and medullary carcinoma of the thyroid of the lungs that secrete **proteins that resemble the structure of ACTH**, therefore, the adrenal glands undergo **bilateral cortical hyperplasia** and secrete Corticosteroids and when this happens the patient comes with Cushing syndrome. Note that any nodular hyperplasia in the gland, means it's ACTH dependent.

The biochemical hallmark of adrenal Cushing syndrome is **elevated levels of cortisol with low serum levels of ACTH**

Morphology:

Could be one of the following abnormalities: **in pituitary** or **in adrenal gland**

In pituitary:
The most common alteration is termed **Crooke hyaline change** (most common): accumulation of intermediate **keratin filaments** in the cytoplasm of the ACTH-producing cells → resulting from ↑ endogenous or exogenous glucocorticoids.

In adrenal glands:
Morphologic changes depend on the cause of the **hypercortisolism;** it could be:

1. Bilateral Cortical atrophy: results from **exogenous glucocorticoids**.
2. Diffuse hyperplasia: individuals with **ACTH-dependent Cushing syndrome**
3. Macronodular or micronodular hyperplasia. (Primary cortical hyperplasia)
4. Adenoma or carcinoma. (one of the glands will has the tumor & the other will be atrophied)

The adenoma is distinguished from nodular hyperplasia by its solitary, circumscribed nature.
1- Bilateral atrophy → because the ACTH is inhibited by the exogenous steroid
2- Bilateral diffuse hyperplasia (DIFFUSE hyperplasia so it's ACTH dependent Cushing)
3- Adenoma or carcinoma (solitary mass mostly)

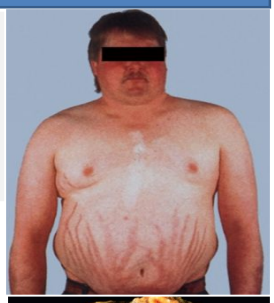
[2] Relative Frequency
[3] Ratio of Females to Males

Clinical Features of Cushing Syndrome:

- Obesity or weight gain "truncal obesity"
- Rounded face "Moon-like"
- ↓ libido
- Facial plethora
- Thin skin
- ↓ in linear growth in children
- Hypertension
- Nephrolithiasis
- Hyperglycemia
- Hirsutism "in females"
- Easy bruising
- Mental disturbance (depression, mood swing, frank psychosis)
- Menstrual irregularity
- Proximal muscle weakness and atrophy
- Abdominal striae
- Polydipsia[4]
- Osteoporosis and fractures (bone resorption)
- Increased risks of infections[5]
- Increased pigmentation (in extraadrenal Cushing syndrome)

Cushing syndrome usually develops gradually and may be quite subtle in its early stages. A major exception is Cushing syndrome associated with small cell carcinomas

If we are treating a patient with steroids and we want to stop it, you don't stop it suddenly but the dose should be tapered "**Gradually**" cause there's dependence, if we don't do it this way the patient might get into adrenal crisis, shock, hypotension, severe withdrawal symptoms and flare of the original disease.



Diagnosis:

1. Serum ACTH:
   - Low → Primary cause (adrenal problem).
   - High → Pituitary adenomas and ectopic ACTH. (Secondary cause)
2. High dose dexamethasone suppression test:
   - Suppression of ACTH→ pituitary adenomas.
   - Fail of suppression of ACTH→ ectopic ACTH.

Secretion of cortisol has a **Diurnal "Circadian" pattern**, so if you want to take a sample from a patient you must follow up the rules, sample should be taken from **8-9 am at its peak** "highest" point and then it goes down until 11pm in the evening then we take another sample at night, if it's still high and didn't drop then the patient has a disease of uncontrolled secretion of Cortisol.

Hyperaldosteronism:

Hyperaldosteronism may be **primary** or **secondary** to an extraadrenal cause.

Primary hyperaldosteronism indicates a primary, autonomous overproduction of aldosterone, with resultant **suppression of the renin-angiotensin** system and decreased plasma renin activity. **Causes of Primary hyperaldosteronism:**

- **Bilateral idiopathic hyperaldosteronism**, characterized by bilateral nodular hyperplasia of the adrenal glands. It's the **most common** underlying cause of primary hyperaldosteronism, the pathogenesis is unclear.

- **Adrenocortical neoplasm (Conn syndrome)**, either an aldosterone-producing adenoma (or, rarely, an adrenocortical carcinoma.

- **Rarely, familial hyperaldosteronism** may result from a genetic defect that leads to over activity of the aldosterone synthase gene, CYP11B2.

[4] Abnormally great thirst
[5] Inhibiting phospholipase A2, histamine IL-2 (immunosuppression)

Secondary hyperaldosteronism:

In secondary hyperaldosteronism aldosterone release occurs in response to activation of the renin-angiotensin system.

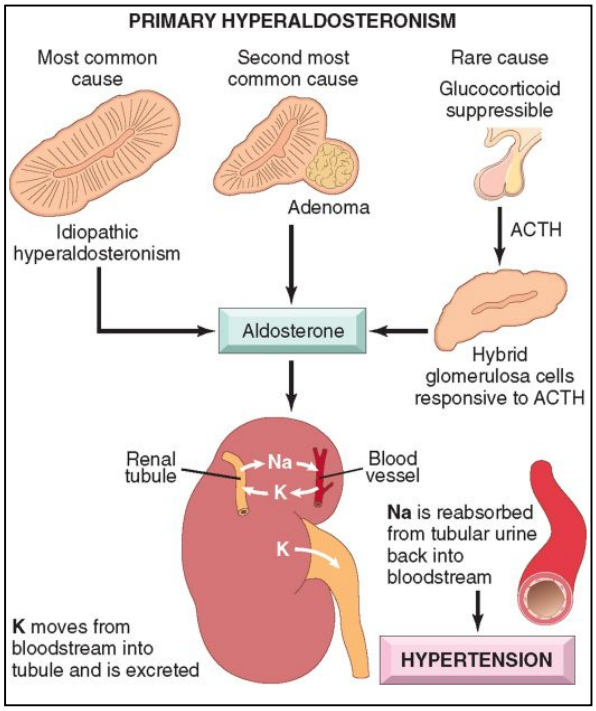
This condition is characterized by **increased levels of plasma renin** and it might present **in association with:**

- ❖ Decreased renal perfusion (arteriolar nephrosclerosis, renal artery stenosis).
- ❖ Arterial hypovolemia and edema (congestive heart failure, cirrhosis, nephrotic syndrome).
- ❖ Pregnancy (caused by estrogen-induced increases in plasma renin substrate).

Clinical Features:

- **Hypertension:** primary **hyperaldosteronism** may be the **most common** cause of **secondary hypertension.**
  The long-term effects of hypertension are:
  1- Cardiovascular compromise (e.g., left ventricular hypertrophy)
  2- ↑ in adverse events, stroke and myocardial infarction.

  This hypertension is curable, once we resect the tumor, it will resolve. PRIMARY hypertension (the most common form of hypertension is PRIMARY "idiopathic")
- **Hypokalemia.**



Morphology (Aldosterone-producing adenomas):

- Aldosterone-producing adenomas are almost always **solitary**, small (well-circumscribed lesions).
- Composed of **lipid-laden** cortical cells more closely resembling **fasciculata cells**
- A characteristic feature of aldosterone-producing adenomas is the presence of
- **Spironolactone bodies.**
- Adrenal cortexes are not atrophic. (Differentiated from Cushing syndrome)

Bilateral **idiopathic** hyperplasia is marked by diffuse or focal hyperplasia of cells resembling those of the normal **zona glomerulosa**.

Aldosterone measurement varies with posture (upright posture stimulates renin secretion)

Adrenocortical hypofunction (adrenocortical insufficiency):

Adrenocortical insufficiency, or hypofunction, may be caused by either **primary**[6] adrenal disease or decreased stimulation of the adrenals resulting from a deficiency of ACTH (**secondary** hypoadrenalism).

Waterhouse-Friderichsen syndrome:

- Steroid withdrawal (that's why we usually stop the steroid therapy gradually .
- Stress with underlying chronic (because stress increase demands of the hormones)

[6] like Addison's

There're 3 patterns of adrenocortical insufficiency:

Primary Acute Adrenocortical Insufficiency (adrenal crisis)

- Persons with **chronic** adrenocortical insufficiency may develop **an acute crisis** after any stress (e.g. infections or trauma), which manifests by intractable vomiting, abdominal pain, hypotension, coma and vascular collapse (Death follows unless treated immediately).
- Happens if steroid treatment is withdrawn too rapidly (because the atrophic glands are unable to respond adequately if an event/stress)
- Massive adrenal hemorrhage:
  - Patients suffering from overwhelming sepsis; it is known as (**Waterhouse-Friderichsen syndrome**), associated with *Neisseria meningitidis* septicemia.
  - Postoperative patients who develop **disseminated intravascular coagulation.**
  - Patients maintained on **anticoagulant therapy**
  - Pregnancy, also occur in neonates following a prolonged or difficult delivery.

Primary Chronic Adrenocortical Insufficiency: Addison Disease

- **Autoimmune adrenalitis**:
  - Previously the **commonest cause was tuberculosis** of the adrenal cortex, but nowadays Autoimmune Adrenalitis is the commonest, as it accounts for 60-70 % of cases.
  - Autoimmune destruction of steroid-producing cells, and autoantibodies to several key steroidogenic enzymes, high serum ACTH.
  - Occurs in one of two autoimmune polyendocrine syndromes: APS1& APS2. (caused by a mutation in **AIRE** Gene)
- **Infections**, particularly tuberculosis and those produced by fungi
- **AIDS:** patients with AIDS are at risk for developing primary chronic adrenocortical insufficiency.
- **Metastatic Neoplasms:** Carcinomas of the **lung and breast** are the source of majority of metastases in the adrenals

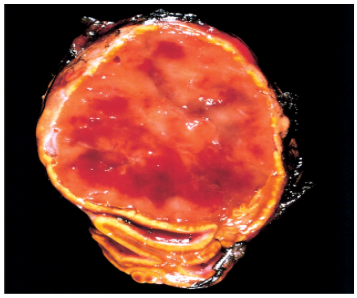
Secondary Adrenocortical Insufficiency

- Any disorder of the **hypothalamus and pituitary**, such as metastatic cancer, infection, infarction, or irradiation, that **reduces the output of ACTH** leads to a syndrome of hypoadrenalism.
- The hyperpigmentation of primary Addison disease is lacking & Low serum ACTH

Clinical Features:

- GIT disturbance, nausea, vomiting, weight loss, and diarrhea.
- Hyperpigmentation in patients with **primary** adrenal disease (increased levels of ACTH precursor hormone stimulate melanocytes, with resultant hyperpigmentation of the skin and mucosal surfaces, in the 2°, aldosterone is not affected because it is ACTH independent).
- Hyperkalemia, hyponatremia, volume depletion, and hypotension,
- **Secondary hypoadrenalism** is characterized by deficient cortisol and androgen output but normal or near-normal aldosterone synthesis.
- Hypoglycemia occasionally may occur, hypotension and dehydration.

Pheochromocytoma:



This is a **functioning tumor** derived from the chromaffin cells of the adrenal medulla, and is classified as **a paraganglioma.**

The presence of a pheochromocytoma should be suspected in any young hypertensive patient and, although rare, is one of the curable causes of hypertension.

Rule of 10	▪ 10% of these tumors are associated with familial syndromes such as **multiple endocrine neoplasia (MEN)** syndrome. (Also von-Hippel-Lindau disease, von Recklinghausen's disease, tuberous sclerosis, and Sturge-Weber syndrome.) ▪ 10% of pheochromocytomas are extra-adrenal. ▪ 10% of nonfamilial adrenal pheochromocytomas are bilateral; this figure may rise to 70% in cases that are associated **with familial syndromes.** ▪ 10% of adrenal pheochromocytomas are biologically malignant. ▪ 10% of adrenal pheochromocytomas in childhood.
Exceptions to the rule of 10 (Mutations)	**25% of people with pheochromocytomas and paragangliomas harbor a germ line mutation in one of the following genes:** - **RET**, which causes type 2 MEN syndrome. - **NF1**, which causes neurofibromatosis. - **VHL**, which causes Von-Hippel-Lindau disease. - 3 genes encoding subunits within the succinate dehydrogenase complex (**SDHB, SDHC and SDHD**), which is involved in mitochondrial oxidative phosphorylation.
Diagnosis	The diagnosis of phaeochromocytoma is based on estimating the urinary excretion of the **catecholamine metabolite vanillylmandelic acid (VMA**), which is at least doubled when the tumor is present.
Morphology	▪ Small to large hemorrhagic. ▪ Highlighted by a variety of silver stains. ▪ Granules containing catecholamines. ▪ Polygonal to spindle shaped chromaffin, (chief cells). ▪ Sustentacular small cells. ▪ **Zellballen nests.** ▪ Well demarcated. **Grossly:** ❖ yellow-tan, well-defined lesions. ❖ Incubation of the fresh tissue with potassium dichromate solutions turns the tumor dark brown.

Note that the definitive diagnosis of **malignancy** in pheochromocytomas is based exclusively on the presence of metastases.

Clinical features:

- **Overproduction** of catecholamines produces isolated paroxysmal episodes of **hypertension**, associated with headaches, sweating, palpitations, pallor, anxiety and nausea.
- Pain in the abdomen or chest, nausea, and vomiting.
- ↑ risk of myocardial ischemia, heart failure, renal injury, and stroke (cerebrovascular accident). Sudden cardiac death may occur, probably secondary to catecholamine-induced myocardial irritability and ventricular arrhythmias.
- In some cases, pheochromocytomas secrete other hormones such as ACTH and somatostatin and may therefore be associated with clinical features related to the effects of these and other peptide hormones

Zellballen nest:

- Centrally it has polyhedral cell with abundant amphiphilic cytoplasm and sustentacular cells "flat" in the periphery.
- Between the nests there's fibrovascular cords

Clinical features:

- Hypertension, headache, palpitation, sweating and tremors.
- Laboratory findings.
- Increased urinary excretion of free catecholamines and their metabolite.

Further Reading: (Read it just in case)

- **MEN 2A: Parathyroid** hyperplasia, **Pheochromocytoma and** Medullary thyroid carcinoma (secretes calcitonin)
- **MEN 2B:** Pheochromocytoma, Medullary thyroid carcinoma (secretes calcitonin) and neuromas

Adrenocortical Carcinoma:

Difficult to diagnose cause the criteria are not like other malignancies. We rely on increased weight of adrenal gland, normally adrenal glands weigh 4g, if someone has cortical nodular hyperplasia it will reach 6 grams, but if there's significant increase in adrenal gland weight "reaching up to 500 g" think about adenocarcinoma cell atypia and **pleomorphism is not really important** here for diagnoses of glands" **invasion** and increased in size and weight of the adrenal gland are important.

Congenital adrenal hyperplasia (CAH):

- Associated with increased androgens, & deficiency of cortisol & aldosterone.
- It can be seen in children, caused by Deficiency of certain enzymes, especially, **21 or 11 hydroxylase enzymes.**
- In kids, manifested as ambiguous genitalia "has both genitals a vagina and a penis".
- If the deficiency is partial "incomplete mutation of the gene" e.g. female has precocious puberty, hirsutism, hoarseness of voice.
- Neonatal screening of those enzymes plays a major rule for improving healthcare.
- Adrenal medullary cells are from neural origin and they resemble the ganglion cells.

Hypersecretion of sex steroids:

The adrenal cortex can secrete excess androgens in either of two settings:

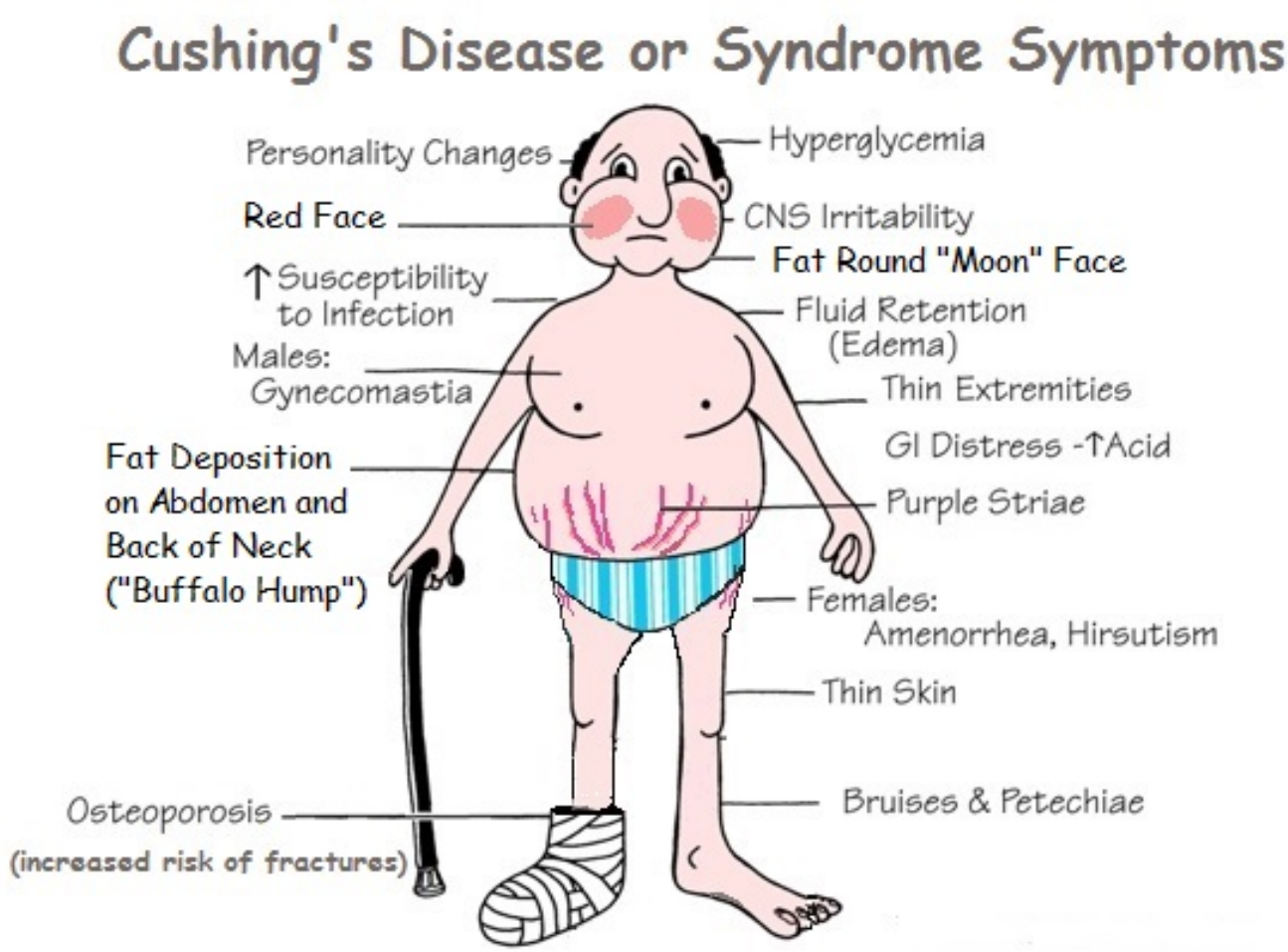
- adrenocortical neoplasms (usually virilizing carcinomas) or congenital adrenal hyperplasia (CAH).
- CAH consists of a group of autosomal recessive disorders characterized by defects in steroid biosynthesis, usually cortisol; the most common subtype is caused by deficiency of the enzyme 21-hydroxylase.
- Reduction in cortisol production causes a compensatory increase in ACTH secretion, which in turn stimulates androgen production.
- Androgens have virilizing effects, including masculinization in females (ambiguous genitalia, oligomenorrhea, hirsutism), precocious puberty in males.

TABLE 24-10 -- Adrenocortical Insufficiency

PRIMARY INSUFFICIENCY
Loss of Cortex
Congenital adrenal *hypo*plasia
X-linked adrenal hypoplasia (*DAX1* gene on Xp21)
"Miniature"-type adrenal hypoplasia (unknown cause)
Adrenoleukodystrophy (*ALD* gene on Xq28)
Autoimmune adrenal insufficiency
Autoimmune polyendocrinopathy syndrome type 1 (*AIRE1* gene on 21q22)
Autoimmune polyendocrinopathy syndrome type 2 (polygenic)
Isolated autoimmune adrenalitis (polygenic)
Infection
Acquired immune deficiency syndrome
Tuberculosis
Fungi
Acute hemorrhagic necrosis (*Waterhouse-Friderichsen syndrome*)
Amyloidosis, sarcoidosis, hemochromatosis
Metastatic carcinoma
Metabolic Failure in Hormone Production
Congenital adrenal *hyper*plasia (cortisol and aldosterone deficiency with virilization)
Drug- and steroid-induced inhibition of ACTH or cortical cell function
SECONDARY INSUFFICIENCY
Hypothalamic Pituitary Disease
Neoplasm, inflammation (sarcoidosis, tuberculosis, pyogens, fungi)
Hypothalamic Pituitary Suppression
Long-term steroid administration

Note that Dr. Amani read this whole table & mentioned that we don't need to memorize the mutations

Extra


Cushing's Disease or Syndrome Symptoms
Personality Changes
Red Face
↑Susceptibility to Infection
Males: Gynecomastia
Fat Deposition on Abdomen and Back of Neck ("Buffalo Hump")
Osteoporosis
(increased risk of fractures)
Hyperglycemia
CNS Irritability
Fat Round "Moon" Face
Fluid Retention (Edema)
Thin Extremities
GI Distress -↑Acid
Purple Striae
Females: Amenorrhea, Hirsutism
Thin Skin
Bruises & Petechiae

Check Your Understanding

MCQs:

1- Most common cause of Cushing syndrome is:

A- Iatrogenic
B- Ectopic
C- Pituitary adenoma
D- Adrenal carcinoma

2- Most common cause of endogenous Hypercortisolism is:

A- Bronchial carcinoid tumor
B- Pituitary adenoma
C- Adrenal adenoma
D- Conn's syndrome

3- Which of the following are 2 surgically correctable forms of hypertension?

A- Pheochromocytoma and idiopathic hyperaldosteronism
B- Aldosterone-producing adenoma and Cushing syndrome
C- Pheochromocytoma and Aldosterone-producing adenoma
D- Addison's disease and virilizing syndromes

4- All of the following are related to hypofunctional states except:

A- Waterhouse-Friderichsen syndrome
B- myxedema
C- insulin-dependent diabetes mellitus (type 1)
D- Conn's syndrome

5- A 60-year-old woman with small cell carcinoma of the lung notes rounding of her face, upper truncal obesity, and muscle weakness. Physical examination reveals thin, wrinkled skin, abdominal striae, and multiple purpuric skin lesions. The patient's blood pressure is 175/95 mm Hg. Laboratory studies will likely show elevated serum levels of which of the following hormones?

A- Aldosterone
B- Corticotropin
C- Epinephrine
D- Prolactin

1-A
2-B
3-C
4-D
5-B

6- Which of the following is true regarding pheochromocytoma?

A. It is usually an aggressive, malignant tumor
B. It only occurs in the adrenal gland
C. It is derived from neural crest cells
D. Many tumors have a 1p deletion

7- A patient with Cushing syndrome might present with any of the following EXCEPT:

A. Obesity
B. A buffalo hump
C. Moon facies
D. Hyperpigmented skin

8- Known as chronic adrenal insufficiency, hypocortisolism or hypocorticism, a rare endocrine disorder in which the adrenal gland produces insufficient amounts of steroid hormones (glucocorticoids and often mineralocorticoids):

A- Cushing's syndrome
B- Conn's syndrome
C- Addison's disease
D- Waterhouse-Friderichsen syndrome

9- Some regard this as the complications of meningococcal septicemia but others are more specific that it is haemorrhage into the adrenal glands.

A- Addison's disease
B- Cushing's syndrome
C- Waterhouse-Friderichsen syndrome
D- Conn's syndrome

10- When a pituitary tumor secretes excessive ACTH, the disorder resulting from this is referred to as:

A- Cushing's disease
B- Conn's syndrome
C- Addison's disease
D- Cushing's syndrome

6-C
7-D
8-C
9-C
10-A

Contact us: Pathology435@gmail.com

Team Members:

فهد العبداللطيف نوف التويجري

محمد الدغيثر	الجوهرة المزروع	فتون الصالح
معاذ باعشن	إلهام الزهراني	كوثر الموسى
تركي الناصر	بدور جليدان	لميس آل تميم
عبدالرحمن الزامل	دانيا الهنداوي	لولوه الصغيّر
محمد الزاحم	دانة عمله	مريم سعيدان
عبدالعزيز الزيدان	ديما الفارس	منيرة العيوني
عبدالله الفريح	رزان السبتي	مي العقيل
ماجد العسبلي	سارة القحطاني	نورة الخراز
عبدالله العليوي	شماء السعد	نورة الطويل
عبدالرحمن الناصر		نورة الخيال

قال صلى الله عليه وسلم: {من سلك طريقًا يلتمس فيه علمًا سهَّل الله له بهِ طريقًا إلى الجنة}

دعواتنا لكم بالتوفيق
