NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS
MEDICAL SCHOOL

Adrenal disorders

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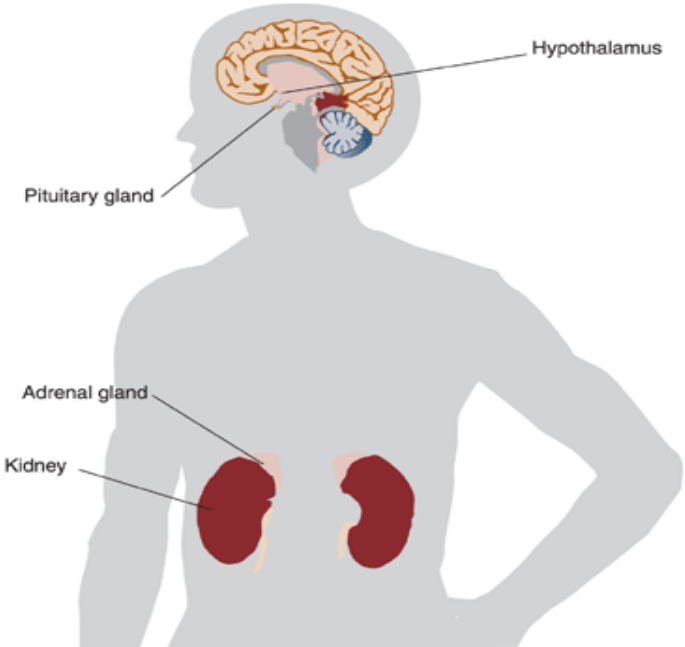
Adrenal disorders

- We will discuss the adrenal glands' anatomy, physiology, and biochemistry.
- We will explain the function of the Hypothalamic-pituitary-adrenal axis (HPA axis)
- We will describe the clinical approach and management of adrenal disorders (hyper- and hypo-secretion of hormones)
- Addison’s disease.
- Cushing syndrome.
- Hyperaldosteronism.
- Pheochromocytoma.

Hypothalamic-Pituitary-Adrenal (HPA) Axis

- The hypothalamus releases CRH in response to inadequate serum cortisol levels
- When cortisol is low, CRH is released
- CRH stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH)
- ACTH signals the adrenal glands to release cortisol.
- When cortisol levels return to normal, there is a negative signal (negative feedback) that mitigates additional ACTH production.



Anatomy of the adrenal glands

- Adrenal glands are paired, pyramid-shaped organs on top of the kidneys
- They are composed of the **Adrenal Cortex** (80-90%)– a glandular tissue derived from embryonic mesoderm
- And the **Adrenal Medulla** (10-20%)– formed from neural ectoderm, can be considered a modified sympathetic ganglion.

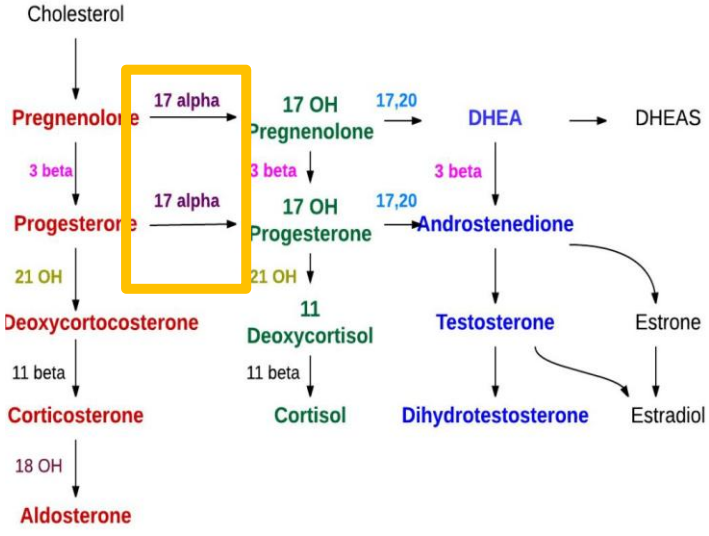
- The **Cortex** has three zones:
- ➢ Zone glomerulosa } Produces mineralocorticoids
- ➢ Zone fasciculata
- ➢ Zone reticularis } Produce cortisol and androgens.

- The **Medulla** secretes catecholamines, which mediate the stress response.

✓Norepinephrine
✓Epinephrine
✓Dopamine

Adrenal Cortex Hormonal Secretion

- **Zone glomerulosa**:
- ➢ produces aldosterone
- There is no 17-hydroxylase activity
- The renin-angiotensin system and potassium levels primarily regulate aldosterone synthesis.
- **Zone fasciculata and reticularis:**
- ➢ Produce cortisol, androgens, and small amounts of estrogens.
- For these productions, 17-hydroxylase is necessary
- This hormonal production is regulated by ACTH.



Aldosterone actions

- Stimulates sodium reabsorption by the distal tubule and collecting duct of the nephron and promotes potassium and hydrogen ion excretion
- Increases transcription of Na/K pump
- Increases the expression of apical Na channels and an Na/K/Cl co-transporter
- Expands the extracellular volume

Absoption χανεται το r

Aldosterone secretion

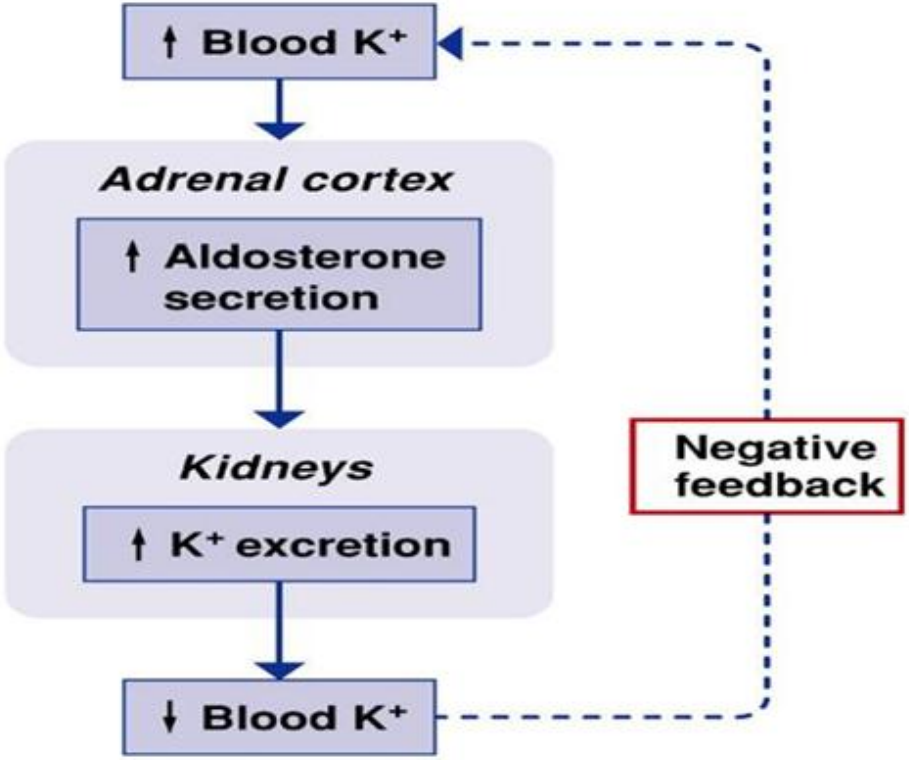
- **Aldosterone secretion is stimulated by:**

1. Decreased blood volume or pressure. Then, the renin-angiotensin system is activated to maintain hemodynamic stability

2. Rising blood levels of K+

3. Low blood Na+

Increased Potassium and Aldosterone



εξκριτιον

Glucocorticosteroids-cortisol

Frequently referred to as the ‘stress hormone’

Released in response to physiological or psychological stress

Examples: exercise, illness, injury, starvation, extreme dehydration, electrolyte imbalance, emotional stress, surgery, etc.

Common Adrenal Diseases

Hyperaldosteronism

Causes

- ***Adenoma*** of the adrenal cortex glomerulosa cells. It is usually unilateral
- ***Bilateral adrenal hyperplasia***
- ***Adrenal carcinoma*** (rare)

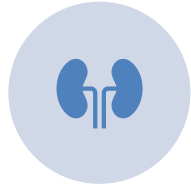
Two distinct entities should be discriminated between: Primary hyperaldosteronism and secondary hyperaldosteronism. Primary hyperaldosteronism is related to increased (autonomous) production of aldosterone, leading to renin suppression. Secondary hyperaldosteronism is associated with increased renin following low blood pressure or hemodynamic instability. High renin leads to increased aldosterone production.

Cause	Renin	Aldosterone	Example
Primary hyperaldosteronism	Low	High	**Conn's syndrome**, Idiopathic bilateral adrenal hyperplasia
Secondary hyperaldosteronism	High	High	Inadequate renal perfusion (diuretic therapy, cardiac failure, liver failure, nephrotic syndrome, renal artery stenosis)

Clinical Features-Laboratory evaluation

SERUM ALDOSTERONE **IS INCREASED**

LOW RENIN IN THE PRIMARY DISEASE



PROBABLY LOW POTASSIUM, HIGH SODIUM

CARDIAC ULTRASOUND, ELECTROCARDIOGRAM (ECG)

THE INITIAL SCREENING IS DONE BY CALCULATING THE RATIO OF SERUM ALDOSTERONE TO PLASMA RENIN

1. Hypertension with accompanying hypokalemia.

2. Hypertension at a young age or a history of stroke at a young age (<40 years).

3. Do not forget to check for an adrenal adenoma every time you find an adrenal mass in abdominal imaging tests.

Masses of the adrenal glands incidentally found in imaging tests are called Incidentalomas.

Adrenal insufficiency-Addison's disease

Etiology according to the HPA axis

- **Primary**: defect in the adrenal gland itself

a. Classic Congenital Adrenal Hyperplasia (There is 21-hydroxylase deficiency)
b. Autoimmune destruction
c. Adrenal Hemorrhage

- **Secondary**: Hypopituitarism

a. Rare congenital disorder characterized by abnormal development of the pituitary gland
b. Surgical disturbance or irradiation around the pituitary (i.e, irradiation of a brain cancer)
c. Infiltrative disease, such as histiocytosis
d. Exogenous sources of steroids

- **Tertiary**: hypothalamic defect

In primary adrenal insufficiency, low cortisol and aldosterone levels are found because of the adrenal destruction.

In secondary disease, where the pituitary gland is defective, only cortisol levels are reduced due to a lack of ACTH production. On the other hand, aldosterone levels remain intact, as its production is not ACTH dependent.

Causes	

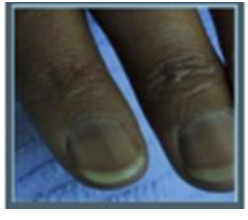
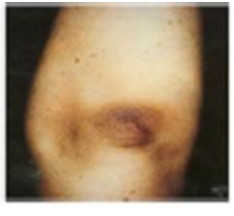
Major	• **Idiopathic atrophy (autoimmune) 80%:**
	  ○ DR. Thomas Addison in 1849, TB was the commonest cause, **now autoimmune is the most common cause.** Addison's disease is more common in women 2.6:1. It is usually diagnosed in the 3rd to 5th decade.
	  ○ Idiopathic addison's disease is **frequently accompanied by other immunological and autoimmune endocrine disorders** e.g. **hyperthyroidism**, **hypothyroidism**, **hashimoto**, **anemia** and **gonadal failure**. One or more of these disorders is usually present in **40-53%** of patients with idiopathic addison's disease.
	  ○ Often positive adrenal antibodies ,Could be an isolated problem or associated with other autoimmune diseases:
	  ■ **Type I** (APECED) : **affects children**: Adrenal insufficiency, hypoparathyroidism, pernicious anaemia, chronic candidiasis, chronic active hepatitis, and hair loss)
	  ■ **Type II** (Schmidt's syndrome) **usually affects young adults** : hypothyroidism, adrenal insufficiency and diabetes mellitus, vitiligo
	• **Tuberculosis 20%**

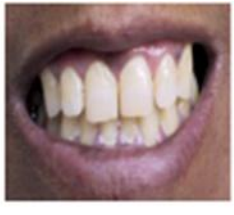
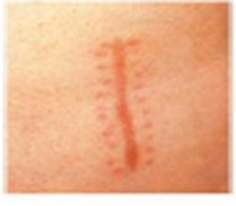
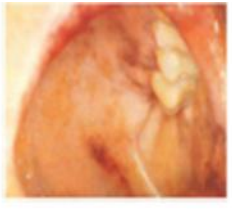
Other	• **Infection** (fungal: Histoplasmosis, CMV HIV, Syphilis, ..etc)
	• **Infiltration** (lymphoma, Hemochromatosis, Amyloidosis, Sarcoidosis, malignancy)
	• **Iatrogenic** (Surgical adrenalectomy, Anticoagulation and hemorrhage)
	• **Medications:** ketoconazole, rifampin, phenytoin, Phenobarbital, Mitotane(Cytotoxic drugs), Metyrapone(Enzyme inhibitor), Aminoglutethimide.
	• **Hereditary and Congenital diseases:** enzyme defects, hypoplasia, congenital adrenal hyperplasia,adrenal unresponsiveness to ACTH, adrenoleukodystrophy, adrenomyeloneuropathy, Refsum disease, Wolman disease)
	• **Miscellaneous**:
	  ○ Triple A syndrome= Allgrove syndrome
	  ○ Adrenal hemorrhage and infarction
	  ○ Radiation therapy

Clinical presentation

Clinical Features of Adrenal Insufficiency and Adrenal Crisis

Symptoms	Signs	Routine Laboratory Tests
Adrenal insufficiency		
Fatigue	Hyperpigmentation (primary only), particularly of sun-exposed areas, skin creases, mucosal membranes, scars, areola of breast	Hyponatremia
Weight loss	Low blood pressure with increased postural drop	Hyperkalemia
Postural dizziness	Failure to thrive in children	Uncommon: hypoglycemia, hypercalcemia
Anorexia, abdominal discomfort		
Adrenal crisis		
Severe weakness		Hyponatremia
Syncope	Hypotension	Hyperkalemia
Abdominal pain, nausea, vomiting; may mimic acute abdomen	Abdominal tenderness/guarding	Hypoglycemia
Back pain	Reduced consciousness, delirium	Hypercalcemia
Confusion		

Evaluation of suspected adrenal insufficiency

1 Perform a cosyntropin (ACTH) stimulation test to evaluate the intrinsic function of the adrenal cortex.

- Cosyntropin stimulation test is performed by measuring a baseline cortisol level, administering 250 mcg of *cosyntropin* (Cortrosyn®) IV, and measuring cortisol levels at 30 and 60 min.
- Peak cortisol (at any time point) >18 mcg/dL = normal response
- Peak cortisol (at any time point) <18 mcg/dL = adrenal insufficiency

2 If adrenal insufficiency has been confirmed, check a plasma ACTH level to distinguish between primary and central (secondary) adrenal insufficiency.

- Plasma ACTH >50 pg/mL = primary adrenal insufficiency
- Plasma ACTH <30 pg/mL = central (secondary) adrenal insufficiency

Management of adrenal insufficiency

- Cortisol and mineralocorticoids replacement in primary disease

- Cortisol alone in secondary disease

Cushing's syndrome

- **Increased production of cortisol**
- Women-to-men ratio is 8:1
- Age of diagnosis 20-40 yrs.

Cushing's disease *is a specific type of Cushing's syndrome that is attributed to excessive* ***pituitary*** *ACTH secretion due to a* ***pituitary adenoma****.*

Cushing's syndrome

➢ **Adrenal adenomas and carcinomas**

- In such a case, there is an autonomous production of cortisol that is not under pituitary hypothalamic control.

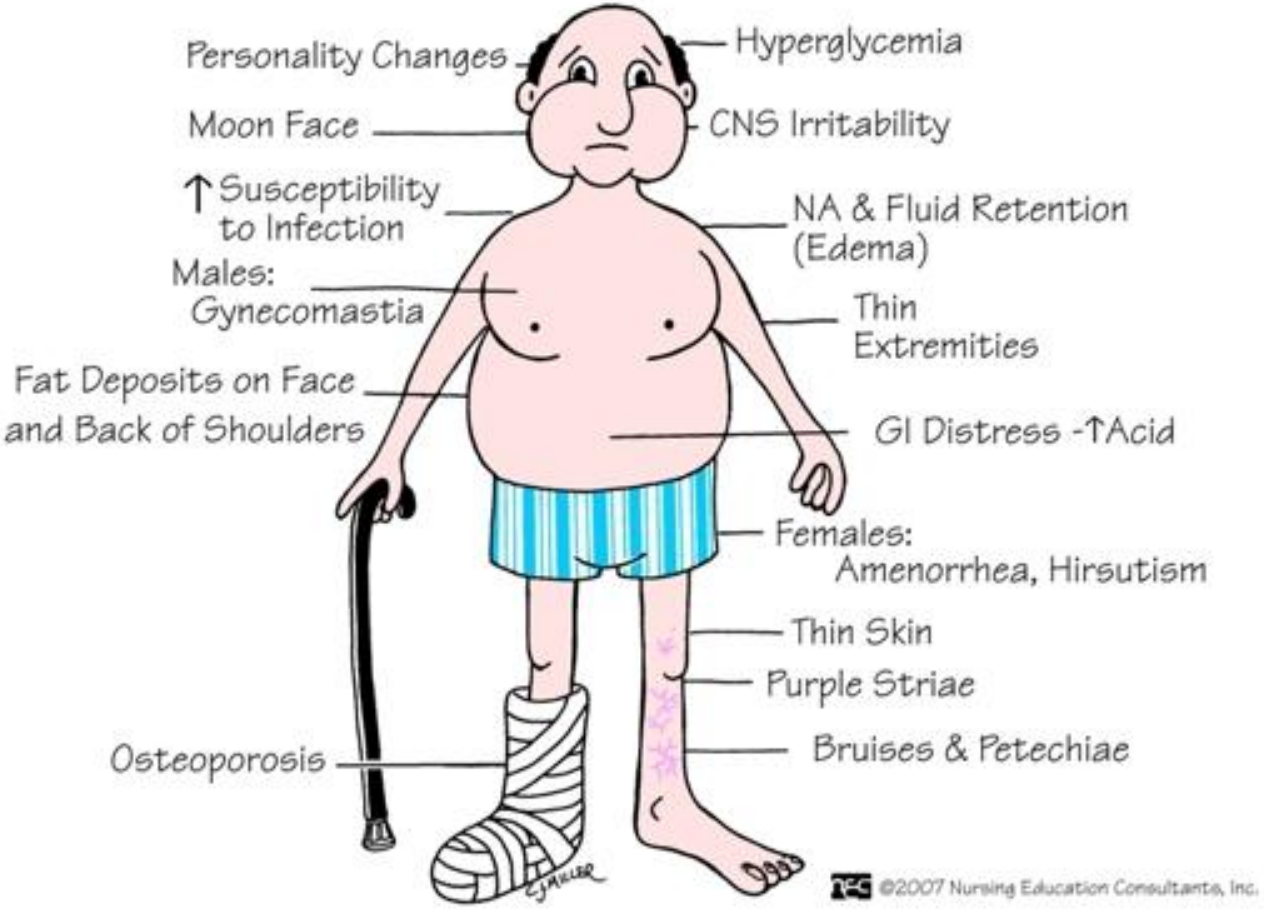
➢ **Ectopic ACTH syndrome:**

Non-pituitary tumors secrete biologically active ACTH.

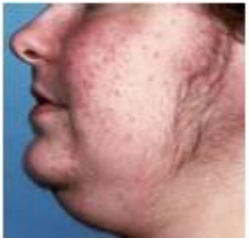
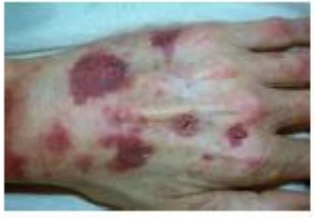
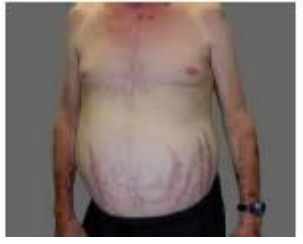
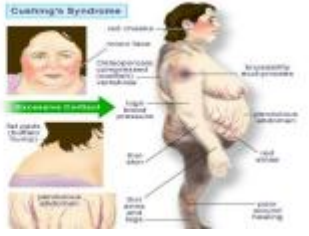
- It is more common in men; the female-to-male ratio is 1:3.
- Peak incidence at the age of 40-60 years.
- It is most common with small cell lung cancer (50% of the cases), but other tumors, e.g., pancreatic cell tumors, carcinoid tumors, etc, may also be implicated.

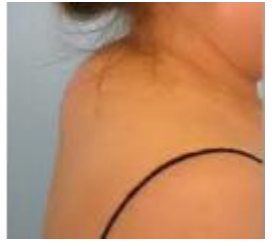
➢ **Exogenous prolonged administration of steroids-** ***Iatrogenic Cushing's syndrome*** ***(the most common)***

CUSHING'S SYNDROME



Signs & Symptoms of Cushing's syndrome



Obesity	• **The most common manifestation** and is classically **central (truncal) affecting mainly the face (moon faced)** with a plethoric appearance, neck, trunk, and abdomen with relative sparing of the extremities. • supraclavicular and dorsal cervical fat pads "**buffalo hump**"
Skin Changes	• There is **thinning of the skin** because of atrophy of the epidermis and underlying connective tissue and facial plethora. • They also have **striae which are classically red to purple** may appear on the abdomen and are due to loss of connective tissue support as well as **easy bruising.** • **Minor wound heal slowly** and they have frequent mucocutaneous fungal infections. • **Hyperpigmentation is common in the ectopic ACTH.**
Hirsutism	• **Facial hirsutism** is most common but it can occur anywhere in the body. • **It is due to the hypersecretion of adrenal androgens.** • **Acne** and seborrhea usually accompany the hirsutism. • Virilism is rare and occur in adrenal carcinoma.

Diagnostic tests for Cushing's syndrome

Increased cortisol in a 24-hour urinary collection

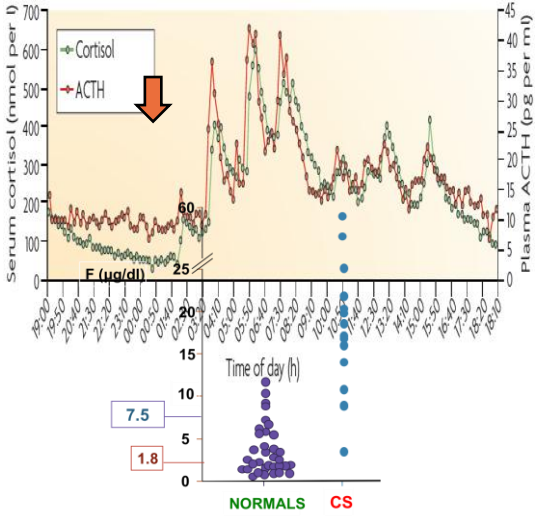
Increased cortisol production in 24 hours

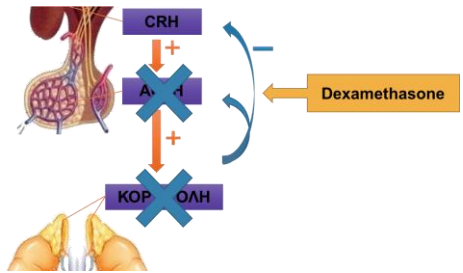
Midnight Cortisol measured in blood or saliva

Abolition of the daily rate of cortisol

Cortisol after suppression test with DEXAMETHASONE

Autonomous cortisol secretion





Cortisol levels follow a diurnal pattern, characterized by high levels at waking, peaks around 30–60 min after waking, and then decrease slowly over the day to the lowest point around bedtime. In Cushing's syndrome, this diurnal rhythm is abolished.

- **The best way of ruling out hypercortisolemia is the dexamethasone suppression test.**

- It is performed by administering 1 mg of dexamethasone at 11 pm and measuring the cortisol levels at 8 am the next morning.

- Normally, the administration of dexamethasone should suppress the ACTH secretion, leading to cortisol reduction.

- However, cortisol levels remain high in cases of autonomous cortisol production (i.e, adrenal adenoma, pituitary adenoma, or ectopic cortisol production).

Treatment MEDICAL

Drug	Mechanism Of Action
Mitotane	acts by inhibiting cortisol synthesis through inhibiting the **P450 enzyme responsible for 11B hydroxylation.**
Metyrapone	The usual drug , also blocks cortisol synthesis by **inhibiting 11B hydroxylase action and also the cholesterol side-chain cleavage.**
Ketocenazole	is a potent **inhibition of the P450 enzymes** with a **principle effect on the 17-20 lyase enzymes but it also inhibits 11B hydroxylase, 18 hydroxylase and cholesterol side-chain cleavage.**

Treatment SURGICAL

- Adrenal tumours:
  - Adenomas are successfully treated by adrenalectomy, while this treatment for carcinoma is usually unsuccessful, and medical therapy can control hypercortisolism in these patients.
- Ectopic ACTH syndrome:
  - Therapy is directed at removing the tumour, which is only successful in the benign tumours; otherwise, drugs that block steroid synthesis can be used, e.g. Metyrapone and mitotane, with steroid replacement if necessary.
- Cushing's disease:
  - Treatment is directed at control of ACTH hypersecretion by the pituitary, and available methods include:
  - Microsurgery -Transsphenoidal surgery with selective removal of the adenoma is the gold standard.
  - Radiotherapy

Pheochromocytoma

- Pheochromocytomas are tumors arising from the chromaffin cells in the sympathetic nervous system.
- They release epinephrine or norepinephrine (or both) and, in some cases, dopamine into the circulation
- 50% are silent. (NO symptoms)

The role of 10:

- 10% bilateral
- 10% Familial
- 10% Malignant
- 10% Extra adrenal

- **Common extra adrenal sites and near the kidneys and the organ of Zuckerkandl.**
- **They can also occur in the posterior mediastinal region.**

**The organ of Zuckerkandl is a small cluster of cells near the adrenal glands. It is typically found near the superior mesenteric artery and the adrenal medulla.

Pheochromocytoma the unusual suspect

- Typical symptoms (tachycardia, palpitations, sweating, headache, and high blood pressure)

Secondary Hypertension (HTN) :

➢ Young age < 40

➢ Difficult to regulate even after taking three or more anti-HTN medications

➢ Resistant HTN

➢ Accelerated HTN

➢ Paroxysmal episodes of high blood pressure

➢ Hypertensive crisis

- If there's any adrenal incidentaloma, you should rule out:
- ➢ Pheochromocytoma
- ➢ Adrenal adenoma responsible for Cushing's syndrome
- ➢ If there is also HTN, you should rule out hyperaldosteronism due to adrenal adenoma

Pheochromocytoma diagnostic tests

- Diagnosis is based on increased plasma free metanephrines (gold standard), or fractionally separated urine metanephrines and normetanephrines (**at least two consecutive 24-hour urine collections).**

- Increased Dopamine in some cases.

Clinical presentation

1	Fatigue or exhaustion	7	Forceful heartbeat with or without tachycardia
2	Tremor	8	Sweating
3	Visual disturbances	9	cold hands and feet
4	Abdominal or chest pain	10	Anxiety or fear of impending death
5	Headache	11	Nausea and vomiting
6	Increased sweating	12	weight loss, constipation

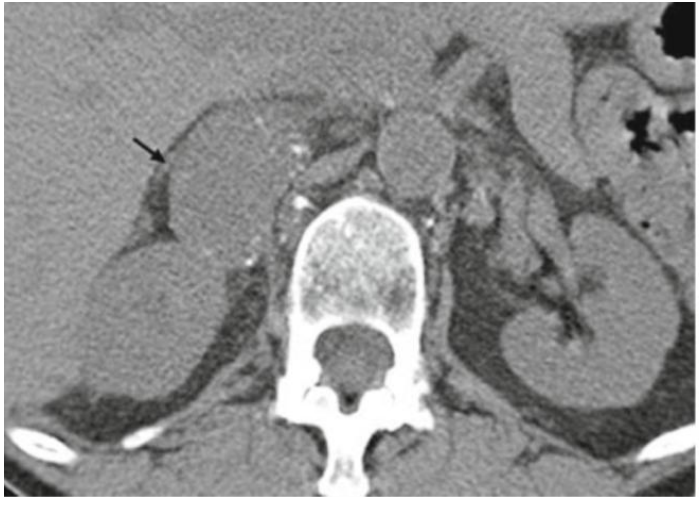
Localization of pheochromocytoma

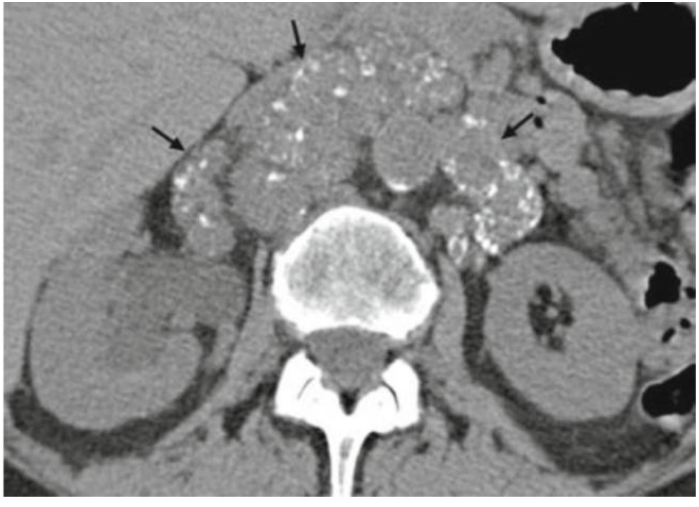
- CT scanning is the radiographic technique of choice compared to other radiological tests.
- MRI is also a very specific and excellent technique for detecting pheochromocytomas.
- MIBG scan. A scintigraphy study using meta-iodo-benzyl-guanidine (norepinephrine analog labeled with iodine) can detect even the smallest tumour by binding to receptors found on phaeochromocytomas. However, not all pheochromocytomas produce detectable images; other tumors, e.g., neuroblastoma, may also give positive images.

❖ Useful in cases of paragangliomas, large size, and malignant features

- Genetic Tests: 30-40% of Pheochromocytoma and Paraganglioma have a positive genetic test.

CT Pheochromocytoma



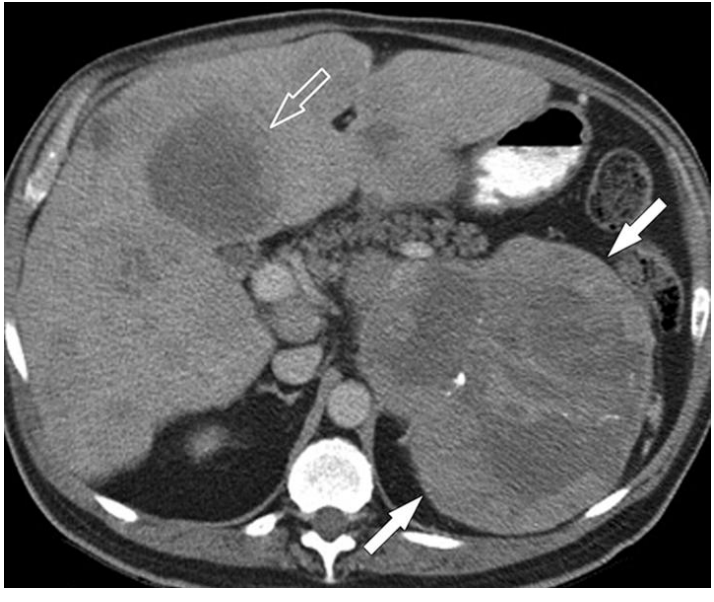


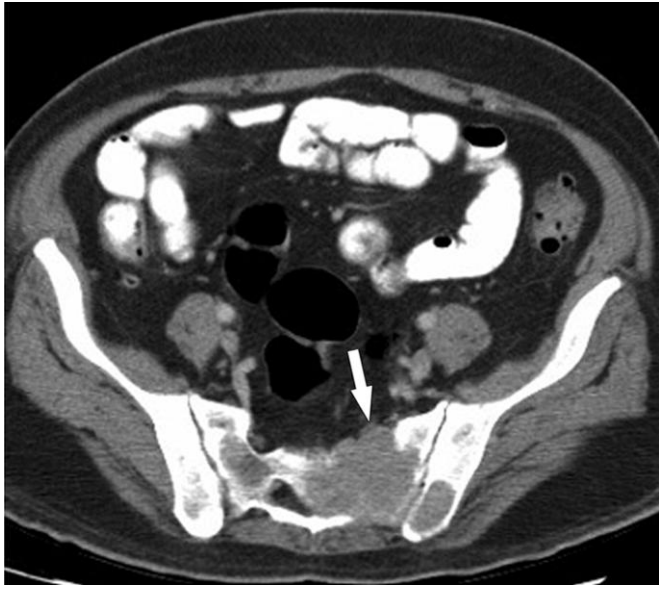
Sensitivity 77%-98%

Specificity 29%-92%

Adrenal or extra-adrenal findings

CT Pheochromocytoma with hepatic metastasis





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Treatment Pheochromocytoma

Surgical tumor resection

Preoperatively

Control HTN

First α-blocker, then β-blocker (10-14 days before operation)

Ca-blockers: can be used

Salt loading: Stabilization of intravascular volume

Oral NaCl: 3 days

Or IVF 0.9% saline 1-2 days before surgery

- Pheochromocytomas secrete catecholamines unpredictably. Surgical manipulation of the tumor can cause a massive release of catecholamines, leading to severe hypertension, cardiac arrhythmias, stroke, and myocardial infarction.

- Alpha-blockers (phenoxybenzamine, doxazosin) are given for 7–14 days preoperatively to control blood pressure and restore blood volume (because the chronic vasoconstriction caused by high catecholamine levels has led to contracted blood volume, increasing the hypotension risk post-surgically.
- Beta-blockers may be added only after alpha-blockade to avoid unopposed alpha-mediated vasoconstriction.

Risk of Postoperative Hypotension

- After tumor removal, catecholamines drop suddenly, risking severe hypotension if volume status is not adequately regulated preoperatively.

Clinical case

- Male, 25 years old, complains of progressive fatigue, weakness, and unintentional weight loss -15kg /4 months.
- Family history:

(+) hypothyroidism (grandfather + two aunts)

- Clinical examination

BP:110/70 mm Hg + 60 bpm, skin = slightly dry

- Laboratory results:

TSH 5,05 ml/L (0,3-4,5)

Clinical case -FOLLOW UP

- T4 treatment (+)
- Four weeks later he complained about increasing fatigue, weakness, dizziness on standing and recent onset of nausea and vomiting

- Physical examination
- Tachycardia (120 bpm)
- BP: 90/60 mm Hg (supine)-80/50 mm Hg (standing)
- Skin = universally tanned, with excessive pigmentation in the folds and palmar.

What from the above are you going to check?

- Laboratory examinations
- Complete blood count (CBC)
- Comprehensive metabolic panel
- Thyroid-stimulating hormone (TSH)
- ACTH
- Cortisol
- Abdominal ultrasound
- Chest radiography
- Computed tomography (CT) scan

Clinical case-Laboratory results

- Cortisol F in serum = 2.2 μg/dl (normal>18 μg/dl)
- Elevated ACTH 639 pg/ml (FT, 9 to 52 pg/ml)
- Anti-TPO, Anti-Tg, APCA (+)

ADDISON DISEASE