433 Teams

MEDICINE

12| Adrenal Gland Disorders

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Objectives:

1. Understand physiology/diseases and management of Hypoadrenalism
2. Understand physiology/diseases and management of Cushing syndrome
3. Understand physiology/diseases and management of Hyperaldosteronism
4. Understand physiology/diseases and management Pheochromocytoma

Adrenal Gland

The adult adrenal glands weighs 8-10gm and lie in the retroperitonium above and medial to the upper poles of the kidneys. A fibrous capsule surrounds the gland. The yellowish outer cortex comprises 90% of the adrenal weight and the inner medulla about 10%.

The outer cortex has three zones:

Zona glomerulosa

Zone fasiculata

Zona reticularis

The inner two zones function as one unit, both producing cortisol and androgens while the zona glumorulosa produces mineralocorticoids

The zona fasiculata and reticularis are regulated by ACTH
Excess or deficiency of this hormone alters the structure and function of the zones i.e. both zones atrophy when ACTH is deficient and when ACTH is present in excess, hyperplasia and hypertrophy of these zones occur.

Regulation of Secretion:

- **Circadian Rhythm**

Regulates both the magnitude and the number of CRH and ACTH secretory episodes. Cortisol secretion is low in the late evening and high in the early morning.

- **Stress**
- **Feedback inhibition**

10% of circulating cortisol is free and it is this biologically active cortisol which is regulated by ACTH

Adrenal Insufficiency:

The most common cause of adrenal insufficiency overall (99% of all cases) is abrupt cessation of exogenous glucocorticoids.

causes		
Primary adrenal insufficiency (Addison's disease) 1-Idiopathic 2-Infectious diseases: tuberculosis (most common cause) 3-Iatrogenic (bilateral adrenalectomy) 4-Metastatic disease	**Secondary adrenal insufficiency** 1-Patients on long-term steroid therapy * (This is the most common cause of secondary adrenal insufficiency) 2-Hypopituitarism (rare)	**Tertiary adrenal insufficiency** hypothalamic disease

* When these patients develop a serious illness or undergo trauma, they cannot release an appropriate amount of cortisol because of chronic suppression of CRH and ACTH by the exogenous steroids. Therefore, symptoms of adrenal insufficiency result.

Clinical features:

Lack of cortisol	Low aldosterone (only seen in primary adrenal insufficiency because aldosterone depends on the renin–angiotensin system, not ACTH)
GI symptoms: anorexia, nausea and vomiting, vague abdominal pain, weight loss	Sodium loss, causing **hyponatremia** and **hypovolemia**, which may lead to: • Hypotension, decreased cardiac output, and decreased renal perfusion • Weakness, shock, and syncope
Mental symptoms: lethargy, confusion, psychosis	**Hyperkalemia** (due to retention of potassium)
Hypoglycemia: Cortisol is a gluconeogenic hormone	
Hyperpigmentation: •This is a common finding in primary adrenal insufficiency; not seen in secondary adrenal insufficiency because in secondary adrenal insufficiency ACTH levels are low, not high. • Low cortisol stimulates ACTH and melanocyte-stimulating hormone secretion.	

Most common clinical findings of adrenal insufficiency:
- Weight loss
- Weakness
- Pigmentation
- Anorexia
- Nausea
- Postural hypotension
- Abdominal pain
- Hypoglycemia

Diagnostic Tests:

Patients have :

1. Hypoadrenalism leads to: (**Decreased plasma cortisol level**)

• Hypoglycemia • Hyperkalemia • Metabolic acidosis • Hyponatremia • High BUN

Hyperpigmentation and hyperkalemia appear in primary, not secondary adrenal insufficiency.

2.level of ACTH level

- IF LOW ⟶ pituitary failure
- IF HIGH ⟶ primary adrenal failure

3- Cosyntropln Stimulation Test (definitive test for primary adrenal insufficiency) (Cosyntropin is synthetic ACTH). You measure the cortisol level before and after the administration of cosyntropin .

In Primary Adrenal Insufficiency, Cortisol Does Not Increase Sufficiently

Treatment:

1- Replace steroids with hydrocortisone

2- Fludrocortisone is a steroid hormone that is particularly high in mineralocorticoid or aldosterone-like effect. Fludrocortisone is most useful if the patient still has evidence of postural instability. Mineralocorticoid supplements should be used in primary adrenal insufficiency when the patient is on oral steroids such as cortisone

Adrenal Crisis • an acute and severely symptomatic stage of adrenal insufficiency that can include severe hypotension and cardiovascular collapse, abdominal pain, acute renal failure, and death.

• Any stress (e.g., trauma, infection, surgery) can precipitate an adrenal crisis. • Can be fatal if untreated.

• Treat with IV hydrocortisone, IV fluids (several liters of normal saline with 5% dextrose), and a search for the underlying condition that precipitated the crisis

(abnormal electrolyte in shock patient think about adrenal crisis)

Cushing's Syndrome:

What is the different between Cushing disease and syndrome?

Cushing's syndrome results from excessive levels of glucocorticoids due to any cause.

Cushing's disease results from pituitary (pituitary adenoma).

causes		
1-Iatrogenic Cushing's syndrome is the most common cause is due to prescribed prednisone or other steroids. Androgen excess is absent (because the exogenous steroid suppresses androgen production by the adrenals).	**2-ACTH-secreting adenoma of the pituitary** (Cushing's disease) **is the second most common cause** and leads to bilateral adrenal hyperplasia. Androgen excess is common.	**3-Adrenal adenomas and carcinomas** (10% to 15%) **4-Ectopic ACTH production**

Clinical features:

- Upper body obesity with thin arms and legs
- Buffalo Hump
- Red, Round Face
- High Blood Sugar
- High Blood Pressure
- Vertigo
- Blurry Vision
- Acne
- Female Balding
- Water Retention
- Menstrual Irregularities
- Thin Skin and Bruising
- Purple Striae
- Poor Wound Healing
- Hirsutism
- Severe Depression
- Cognitive Difficulties
- Emotional Instability
- Sleep Disorders
- Fatigue

"Minnie G", Dr. Cushing's first patient

Remember

Effects of cortisol (generally catabolic)

- **Impaired collagen production, enhanced protein catabolism**
- **Anti-insulin effects (leading to glucose intolerance)**
- **Impaired immunity (has inhibitory effects on PMNs, T cells)**
- **Enhances catecholamine activity (HTN)**

cortisol in excess act as minraloaldesteron =they have all react of hypertension and abnormal electrolyte

Diagnostic Tests:

Establish the Presence of Hypercortlsolism

The best initial test for the presence of hypercortisolism the 24-hour urine cortisol.

The 24-hour urine cortisol is a more specific test of hypercortisolism.

If the 24-hour urine cortisol is *elevated*, the presence of hypercortisolism is confirmed

The second option 1 mg overnight dexamethasone suppression test.

*Causes of **false positive*** 1 mg overnight suppression testing: • Depression • Alcoholism • Obesity

Establish the Cause of Hypercortisolism

ACTH testing is the best initial test to determine the cause or location of hypercortisolism.

If the ACTH level is **elevated**, the cause could be from:

- Pituitary (suppresses with high dose dexamethasone)
- Ectopic production: lung cancer, carcinoid (dexamethasone does not suppress)

Treatment:

*Surgically remove the source of the hypercortisolism

*Transphenoidal surgery is done for pituitary sources whereas laparoscopic removal is done for adrenal sources

TABLE 4-2 Response to Diagnostic Tests in Cushing's Syndrome

Healthy patient	• Normal cortisol/normal ACTH • Suppression with low-dose dexamethasone • Suppression with high-dose dexamethasone • Mild increase with CRH test
Cushing's disease	• High cortisol/high ACTH • No suppression with low-dose dexamethasone • Suppression with high-dose dexamethasone • Great increase in cortisol with CRH test
Adrenal tumor	• High cortisol/low ACTH • No suppression with low-dose dexamethasone • No suppression with high-dose dexamethasone • No change after CRH test
Ectopic ACTH-producing tumor	• High cortisol/high ACTH • No suppression with low-dose dexamethasone • No suppression with high-dose dexamethasone • No change after CRH test

Primary Hyperaldosteronism:

Excessive production of aldosterone

Potassium loss results in **hypokalemia**

Sodium retention, causing ECF volume expansion and HTN

also increases the secretion of hydrogen ions

results in metabolic alkalosis

Remember: Always suspect hyperaldosteronism in a hypertensive patient with hypokalemia who is not on a diuretic

Causes:

1. Adrenal adenoma (in two-thirds of the cases)—aldosterone producing adenoma (Conn's syndrome)
2. Adrenal hyperplasia (in one-third of the cases)—almost always bilateral
3. Adrenal carcinoma (in <1% of the cases)

Clinical features:

1. HTN (most common clinical feature); may otherwise be asymptomatic
2. Headache, fatigue, weakness
3. Polydipsia, nocturnal polyuria (due to hypokalemia)
4. Absence of peripheral edema

High BP + hypokalemia = primary hyperaldosteronism

Diagnostic Tests

The **best initial test** is to measure the ratio of plasma aldosterone to plasma renin.

An elevated plasma renin excludes primary hyperaldosteronism.

The **most accurate test** to confirm the presence of a unilateral adenoma is a sample of the venous blood draining the adrenal. It will show a high aldosterone level.

CT scan of the adrenals should only be done after biochemical testing confirms:

- Low potassium
- High aldosterone despite a high-salt diet
- Low plasma renin level

Treatment

- Unilateral adenoma is resected by laparoscopy.
- Bilateral hyperplasia is treated with eplerenone or spironolactone (Spironolactone causes gynecomastia and decreased libido).

Pheochromocytoma:

1. Pheochromocytomas are rare tumors that produce, store, and secrete catecholamines.
2. Ninety percent found in adrenal medulla (10% extra-adrenal)
3. Curable if diagnosed and treated, but may be fatal if undiagnosed
4. Arise from the chromaffin cells of the adrenal medulla or from the sympathetic ganglia if extra-adrenal.

Clinical features:

1. HTN—BP is persistently high, with episodes of severe HTN (paroxysmal).
2. Severe pounding headache
3. Inappropriate severe sweating
4. Palpitations, with sudden severe HTN
5. Anxiety 6. Feeling of impending doom

Laboratory findings: hyperglycemia, hyperlipidemia, hypokalemia

Rule of 10s for pheochromocytoma tumors

- 10% are familial
- 10% are bilateral (suspect MEN type II)
- 10% are malignant
- 10% are multiple
- 10% occur in children
- 10% are extra-adrenal (more often malignant)— The most common site is the organ of Zuckerkandl, which is located at the aortic bifurcation.

Diagnostic Tests:

The best initial test is the level of free metanephrines in plasma. This is confirmed with a 24-hour urine collection for metanephrines. This is more sensitive than the urine vanillylmandelic acid level.

Direct measurements of epinephrine and norepinephrine are useful as well

-. **Imaging of the adrenal glands with CT or MRI** is done only after biochemical testing

-. **MIBG scanning**: This is a nuclear isotope scan that detects the location of pheochromocytoma that originates outside the adrenal gland

Treatment:

-**Phenoxybenzamine** is an alpha blocker that is the best initial therapy of pheochromocytoma.

- Calcium channel blocker and beta blockers are used afterwards.
- **Pheochromocytoma is removed surgically or by laparoscopy.**

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MEN II A with pheochromocytoma

MCQs

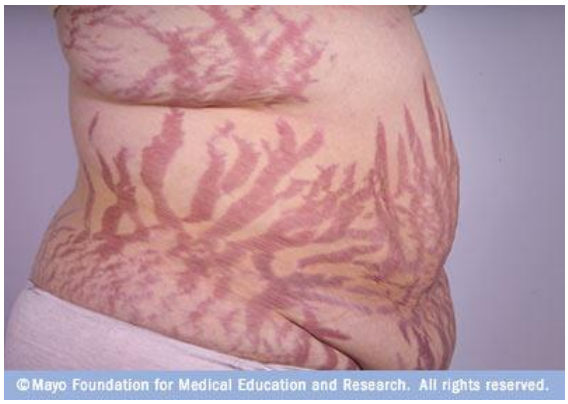
1) A 50-year-old woman is evaluated for hypertension. Her blood pressure is 130/98. She complains of polyuria and mild muscle weakness. She is on no blood pressure medication. On physical examination, the PMI is displaced to the sixth intercostal space. There is no sign of congestive heart failure and no edema. Laboratory values are as follows:
Na^+: 147 mEq/dL
K^+: 2.6 mEq/dL
Cl^-: 112 mEq/dL
HCO_3: 27 mEq/dL
The patient denies the use of diuretics or over-the-counter agents to decrease fluid retention or promote weight loss. She does not eat licorice. Which of the following is the most useful initial diagnostic test?
a. 24-hour urine for cortisol
b. Urinary metanephrine
c. Plasma renin activity
d. Renal angiogram
e. Ratio of serum aldosterone to plasma renin activity

2) A 58-year-old man is referred to your office after evaluation in the emergency room for abdominal pain. The patient was diagnosed with gastritis, but a CT scan with contrast performed during the workup of his pain revealed a 2-cm adrenal mass. The patient has no history of malignancy and denies erectile dysfunction. Physical examination reveals a BP of 122/78 with no gynecomastia or evidence of Cushing syndrome. His serum potassium is normal. What is the next step in determining whether this patient's adrenal mass should be resected?

a. Plasma aldosterone/renin ratio
b. Estradiol level
c. Plasma metanephrines and dexamethasone-suppressed cortisol level
d. Testosterone level
e. Repeat CT scan in 6 months

3) A 25-year-old woman is admitted for hypertensive crisis. The patient's urine drug screen is negative. In the hospital, blood ressure is labile and responds poorly to antihypertensive therapy. The patient complains of palpitations and apprehension. Her past medical history shows that she developed hypertension during an operation for appendicitis at age 23.
Hct: 49% (normal range 37%-48%)
WBC: 11,000/mm3 (4.3-10.8)
Plasma glucose: 160 mg/dL (75-115)
Plasma calcium: 11 mg/dL (9-10.5)
Which of the following is the most likely diagnosis?
a. Panic attack
b. Renal artery stenosis
c. Essential hypertension
d. Type 1 diabetes mellitus
e. Pheochromocytoma

4) The 40-year-old woman shown below complains of weakness, amenorrhea, and easy bruisability. She has hypertension and diabetes mellitus. She denies use of any medications other than hydrochlorothiazide and metformin. What is the most likely explanation for her clinical findings?



a. Pituitary tumor
b. Adrenal tumor
c. Ectopic ACTH production
d. Hypothalamic tumor
e. Partner abuse (domestic violence)

5) A 30-year-old woman has prominent cervical and dorsal fat pads, hirsutism, acne, purple abdominal striae, unexplained hypokalemia, and diabetes mellitus.

a. Acromegaly
b. Exogenous human growth hormone (HGH) use
c. Empty sella syndrome
d. Cushing disease
e. TSH-secreting adenoma
f. Chronic oral glucocorticoid use
g. Prolactin-secreting adenoma

ANSWERS

1- Answer is : e

The patient has diastolic hypertension with unprovoked hypokalemia. She is not taking diuretics. There is no edema on physical examination. Inappropriate aldosterone overproduction is a prime consideration in hypertension with hypokalemia. Hypersecretion of aldosterone increases distal tubular exchange of sodium for potassium with progressive depletion of body potassium. The hypertension is caused by increased sodium absorption. Interestingly, peripheral edema does not occur despite the sodium retention.

2- Answer is : c

This patient has what is commonly referred to as an adrenal incidentaloma. If the mass is greater than 1 cm, the first step is to determine whether it is a functioning or nonfunctioning tumor via measurement of serum metanephrines (pheochromocytoma) and dexamethasone suppressed cortisol (Cushing syndrome) levels. As the patient has no history of malignancy, a CT-guided fine-needle aspiration is not required. The patient has normal BP and potassium: therefore, plasma aldosterone/plasma renin ratio to evaluate primary hyperaldosteronism is not required. There are no signs of feminization or erectile dysfunction, so sex-steroid measurement is not indicated.

3- Answer is : e

Hypertensive crisis in this young woman suggests a secondary cause of hypertension. In the setting of palpitations, apprehension, and hyperglycemia, pheochromocytoma should be considered. Pheochromocytomas are derived from the adrenal medulla. They are capable of producing and secreting catecholamines. Unexplained hypertension associated with surgery or trauma may also suggest the disease. Clinical symptoms are the result of catecholamine secretion. For example, the patient's hyperglycemia is a result of a catecholamine effect of insulin suppression and stimulation of hepatic glucose output.

4- Answer is : a

The clinical findings all suggest an excess production of cortisol by the adrenal gland. Hypertension, truncal obesity, and dark abdominal striae are common physical findings; patients often have ecchymoses at points of trauma (especially legs and forearms) because of increased capillary fragility. The process responsible for hypercortisolism is most often an ACTH-producing pituitary microadenoma. An adrenal adenoma that directly produces cortisol is the next most likely option. Most ectopic ACTH-producing neoplasms (usually small cell carcinoma of the lung) progress too rapidly for the full Cushing syndrome to develop.

5- Answer is : d

Cushing disease produces hypercortisolism secondary to excessive secretion of pituitary ACTH. It often affects women in their childbearing years. Prominent cervical fat pads, purple striae, hirsutism, and glucose intolerance are characteristic features, as well as muscle wasting, easy bruising, amenorrhea, and psychiatric disturbances. Diabetes mellitus can result from chronic hypercortisolism. Exogenous glucocorticoid use will produce cervical fat pads, purple striae, muscle wasting, easy bruising, and secondary diabetes mellitus. Since, however, most oral glucocorticoids (eg, prednisone, dexamethasone) have little mineralocorticoid and no androgenic effect, hypokalemia and hirsutism are rare.

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