Biochemistry Bandits 434

BIOCHEMISTRY OF ADDISON'S DISEASE

OBJECTIVES:

- To identify different causes of primary adreno-cortical hypofunction (Addison's disease)
- To identify secondary causes of adreno-cortical hypofunction
- To understand the diagnostic algorithm for adreno-cortical hypofunction
- To understand the interpretation of laboratory tests of adreno-cortical hypofunction

❖ **Important** ❖ Extra ❖ Biochemistry Edit

ENDOCRINE BLOCK

ALDOSTERONE HORMONE

The principal physiological function of aldosterone is to conserve Na^+, mainly by facilitating Na^+ reabsorption and reciprocal K^+ or H^+ secretion in the distal renal tubule.

Aldosterone is a major regulator of water and electrolyte balance, as well as blood pressure.

Aldosterone, by acting on the distal convoluted tubule of kidney

↑↑ potassium excretion

↑↑ sodium and water reabsorption

THE RENIN - ANGIOTENSIN SYSTEM

useful video

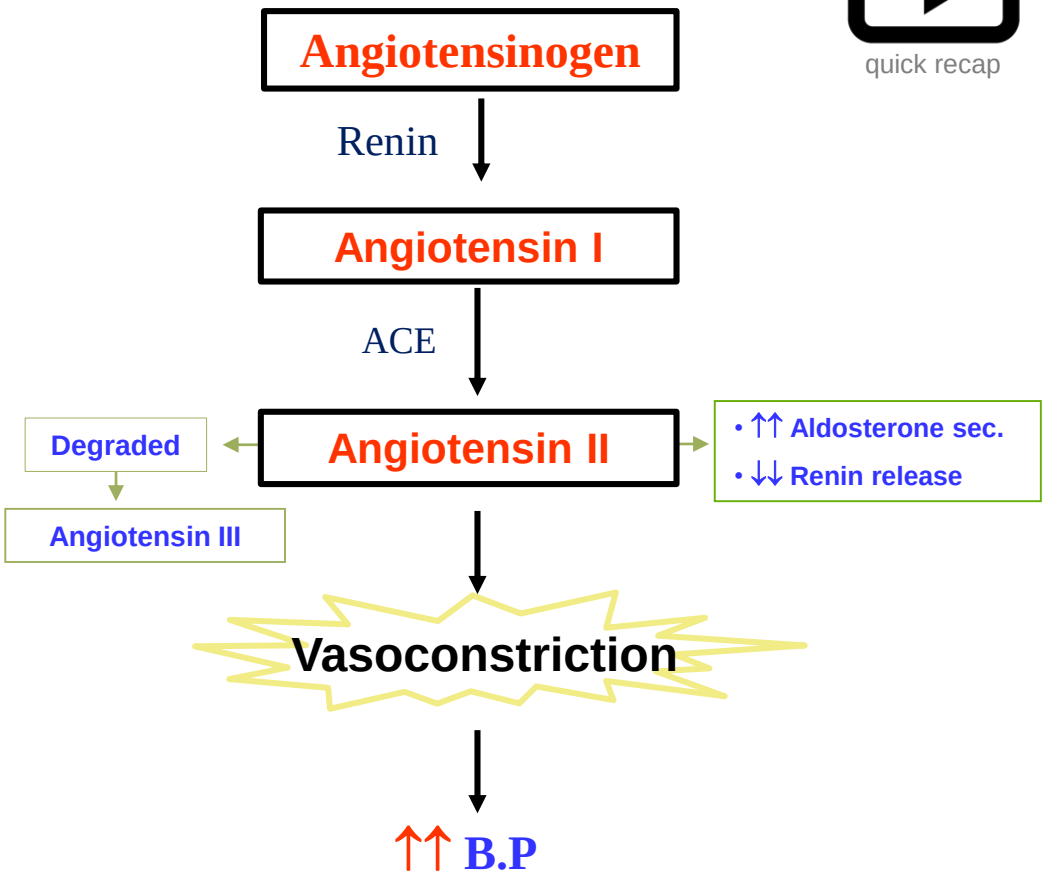
quick recap

- **Renin-Angiotensin system is the most important regulatory mechanism for aldosterone secretion**
- **It is involved in B.P. regulation.**

RENIN:

- A proteolytic enzyme produced by the juxtaglomerular cells of the afferent renal arteriole.
- Sensitive to B.P. changes through baroreceptors
- **released into the circulation in response to :**
  - **a fall in circulating blood volume.**
  - **a fall in renal perfusion pressure** → Stimulates the juxtaglomerular cells.
  - **loss of Na^+** →sensed by macula densa cells

- **Angiotensinogen** α2-Globulin is produced from the **liver**
- **Renin** is produced from the **juxtaglomerular cells** in the kidney, Acts on Angiotensinogen
- **ACE** is produced from the **lungs**, Acts on Ag1



CAUSES OF ADRENOCORTICAL HYPOFUNCTION (AC)

Primary

(destruction of adrenal gland, Addison's disease)

- **Autoimmune**
- **Infection, e.g., tuberculosis**
- **Infiltrative lesions, e.g., amylodosis**

Secondary

- **Pituitary tumors** Ex: nonfunctioning pituitary adenoma
- **Vascular lesions** That would cut the blood supply to the adrenal glands or the pituitary
- **Head trauma**
- **Hypothalmic diseases**
- **Iatrogenic**[1] **(steroid therapy,surgery,radiotherapy)**

1: caused by medical treatment

SIGNS AND SYMPTOMS OF PRIMARY ADRENAL FAILURE (ADDISON'S DISEASE)

❖ **The symptoms are precipitated by trauma, infection or surgery:**

- Lethargy, weakness, nausea & weight loss.
- **Hypotension** especially on standing (postural)
- **Hyperpigmentation** (buccal mucosa, skin creases, scars)
- **Deficiency of both** glucocorticoids and mineralocorticoids
- **Hypoglycemia, ↓ Na^+, ↑ K^+** and raised urea

Na+

K+

- Hyperpigmentation occurs because melanocyte-stimulating hormone (MSH) and (ACTH) share the same precursor molecule, Pro-opiomelanocortin (POMC).
- The anterior pituitary POMC is cleaved into ACTH, γ-MSH, and β-lipotropin.
- The subunit ACTH undergoes further cleavage to produce α-MSH, the most important MSH for skin pigmentation.
- In secondary adrenocortical insufficiency, skin darkening "pigmentation" does not occur.

INVESTIGATION OF ADDISON'S DISEASE (AD)

It's a life threatening disease that needs urgent care. He wont go to the outpatient clinic like cushing's syndrome, he'll go to the ER and will be treated before he is diagnosed.

The patient should be hospitalized → Basal measurement of: Serum urea, Na^+, K^+ & glucose Serum cortisol and plasma ACTH → Definitive diagnosis and confirmatory tests should be done later after crisis.

Screening

- Simultaneous measurement of cortisol and ACTH improves the accuracy of diagnosis of **primary adrenal failure**:

- **Low** serum cortisol <200nmol/L
- **High** plasma ACTH >200 ng/L

- Important: **Normal serum cortisol and UFC [1] (does not exclude AD**.

Confirmatory tests

- Short tetracosactrin (Synacthen) test (Short ACTH stimulation test):
- Measure basal S. cortisol
- Stimulate with I.M. synthetic ACTH (0.25 mg)
- Measure S. cortisol 30 min after I/M injection
- Normal: ↑ **of S. cortisol** to >500 nmol/L

- **Failure of S. cortisol to respond to stimulation, confirm AD**.

- Abnormal results:
  - Emotional stress
  - Glucocorticoid Therapy
  - Estrogen contraceptives.

Other Confirmatory tests

- **Adrenal Antibodies :**

Detection of adrenal antibodies in serum of patients with autoimmune Addison's disease

- **Imaging (Ultrasound/CT)**

Ultrasound or CT for adrenal glands for identifying the cause of primary adrenal failure

1: UFC= urinary excretion of free cortisol

INVESTIGATION OF SECONDARY AC INSUFFICIENCY

No response to short synacthen test: Adrenocortical cells fail to respond to short ACTH stimulation

Screening

- ✓ **Low serum cortisol**
- ✓ **Low plasma ACTH**

Depot Synacthen test:
Measure basal S. cortisol
Stimulate with I.M. synthetic ACTH (1.0 mg) on each of three consecutive days
Measure S. cortisol at 5 hours after I.M. injection on each of the three days

Confirmatory tests

Depot Synacthen test (confirmatory test):

Interpretation of results:

- **Addison's disease:** **No** rise of S. cortisol >600 nmol/L at 5 h after 3rd injection.
- **Secondary AC:** **Stepwise increase** in the S. cortisol after successive injections
- **Limitations:**
  - **Hypothyroidism**: Thyroid deficiency must be corrected before testing of adrenocortical functions
  - **Prolonged steroid therapy**

Other Confirmatory tests

- **Insulin-induced hypoglycemia:**

Adrenal failure secondary to pituitary causes

- **MRI for pituitary gland**

MCQS

1- what can steroid therapy cause?

A. Primary AC hypofunction

B. Secondary AC hypofunction

C. Hyperparathyroidism

2- Renin is produced from:

A. Juxtaglomerular cells

B. Macula densa cells

C. Lung alveoli

3- A 34 year old female comes to the ER because of sever hypotension she feels weak. Her husband told the doctor that she has been loosing weight lately and she becomes tan even without exposing to sun. after investigations the diagnosis was AD. Which of the following tests was used to conform the diagnosis?

A. Depot Synacthen test

B. Insulin-induced hypoglycemia

C. Adrenal antibodies

4- A high ACTH and low blood cortisol levels indicates:

A. Primary renal adenoma

B. AD

C. Secondary pituitary adenoma

5- A 31 year old female was carried to the ER with hypotension crisis the doctor gave her an I.V glucose and infusion. Her family told the doctor that she has sever headache for the last 4 weeks she also experienced some visual disturbance. On investigation we found that she has low ACTH and low Cortisol. What further investigations we would do in order to get the diagnosis?

A. Adrenal antibodies

B. Short ACTH stimulation test

C. MRI

ANSWERS: 1:B , 2:A , 3:C, 4:B, 5:C

SAQS

1- Name 3 symptoms of Addison's:

Lethargy-Hypotension-Hyperpigmentation

2-what are some causes of primary AC hypofunction ?

Autoimmune , tuberculosis, amylodosis

3- explain the reason behind the absence of hyperpigmentation in the secondary AC pituitary adenoma?

Hyperpigmentation occurs because (MSH) and (ACTH) share the same precursor molecule which is (POMC). However in case of secondary AC pituitary adenoma we have low ACTH. In contrast to primary AC we excessive ACTH causing the pigmentation.

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اللهم إني أستودعك ما قرأت وما حفظت وما
تعلمت فرده عند حاجتي إنك على كل شيء قدير

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