Adrenal insufficiency

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Etiology:

- Primary adrenal insufficiency
- Secondary adrenal insufficiency
- Chronic adrenal insufficiency
- Acute adrenal insufficiency

Primary adrenal insufficiency:

- is most commonly caused by autoimmune adrenalitis

1. Isolated autoimmune adrenalitis accounts for 30–40%
2. 60–70% develop adrenal insufficiency as part of autoimmune polyglandular syndromes (APS) → APS1
   → APS2

- congenital adrenal hyperplasia
- Infection/ hemorrhage/ infiltration/ tuberculous adrenalitis/Adrenal metastases (rarely cause adrenal insufficiency, and this occurs only with bilateral, bulky metastases)

Diagnosis	Gene	Associated Features
Autoimmune polyglandular syndrome 1 (APS1)	*AIRE*	Hypoparathyridism, chronic mucocutaneous candidiasis, other autoimmune disorders, rarely lymphomas
Autoimmune polyglandular syndrome 2 (APS2)	Associations with HLA-DR3, CTLA-4	Hypothyroidism, hyperthyroidism, premature ovarian failure, vitiligo, type 1 diabetes mellitus, pernicious anemia
Isolated autoimmune adrenalitis	Associations with HLA-DR3, CTLA-4	
Congenital adrenal hyperplasia (CAH)	*CYP21A2, CYP11B1, CYP17A1, HSD3B2, POR*	

Secondary adrenal insufficiency

- is the consequence of dysfunction of the hypothalamic-pituitary component of the HPA axis
- majority of cases are caused by:

a. Pituitary tumors
b. Pituitary irradiation
c. Pituitary apoplexy/hemorrhage
d. Pituitary infiltration
e. Drug-induced
f. Congenital isolated ACTH deficiency

Clinical Manifestations:

- primary adrenal insufficiency are characterized by the loss of both glucocorticoid and mineralocorticoid secretion
- In secondary adrenal insufficiency, only glucocorticoid deficiency is present
- Adrenal androgen secretion is disrupted in both primary and secondary adrenal insufficiency

Signs and Symptoms of Adrenal Insufficiency

Signs and Symptoms Caused by Glucocorticoid Deficiency

Fatigue, lack of energy
Weight loss, anorexia
Myalgia, joint pain
Fever
Anemia, lymphocytosis, eosinophilia
Slightly increased TSH (due to loss of feedback inhibition of TSH release)
Hypoglycemia (more frequent in children)
Low blood pressure, postural hypotension
Hyponatremia (due to loss of feedback inhibition of AVP release)

Signs and Symptoms Caused by Mineralocorticoid Deficiency (Primary AI Only)

Abdominal pain, nausea, vomiting
Dizziness, postural hypotension
Salt craving
Low blood pressure, postural hypotension
Increased serum creatinine (due to volume depletion)
Hyponatremia
Hyperkalemia

Signs and Symptoms Caused by Adrenal Androgen Deficiency

Lack of energy
Dry and itchy skin (in women)
Loss of libido (in women)
Loss of axillary and pubic hair (in women)

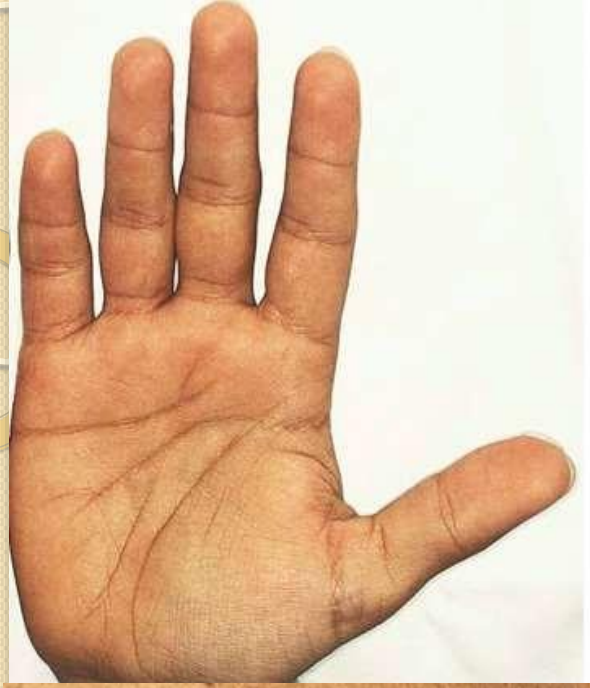
Other Signs and Symptoms

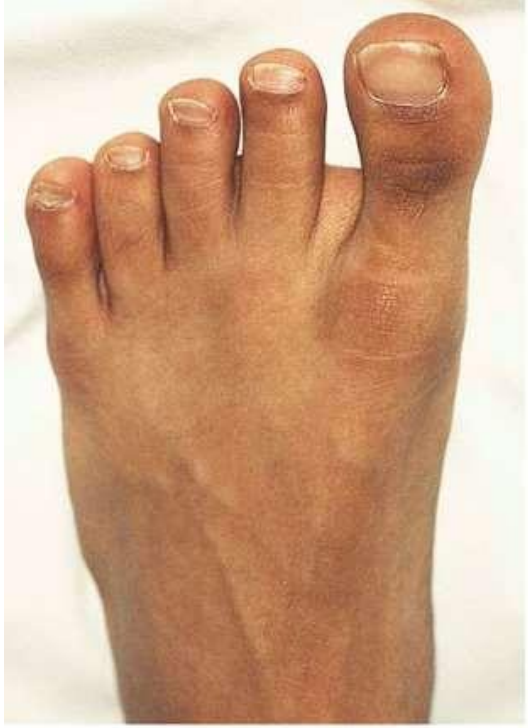
Hyperpigmentation (primary AI only) [due to excess of pro-opiomelanocortin (POMC)–derived peptides]

Alabaster-colored pale skin (secondary AI only) (due to deficiency of POMC-derived peptides)

Chronic adrenal insufficiency

- nonspecific signs and symptoms such as fatigue and loss of energy
- A distinguishing feature of primary adrenal insufficiency is hyperpigmentation, which is caused by excess ACTH stimulation of melanocytes. Hyperpigmentation is most pronounced in skin areas exposed to increased friction or shear stress and is increased by sunlight
- Conversely, in secondary adrenal insufficiency, the skin has an alabaster-like paleness due to lack of ACTH secretion.





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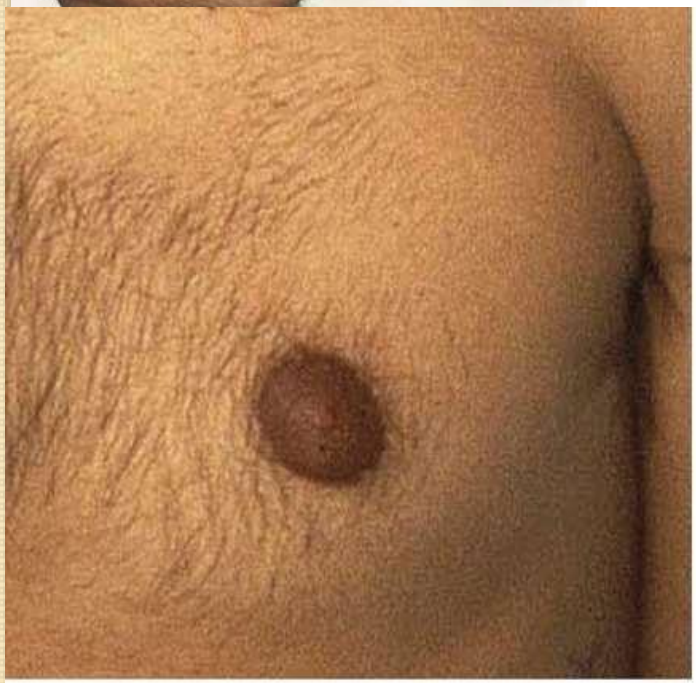
Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com



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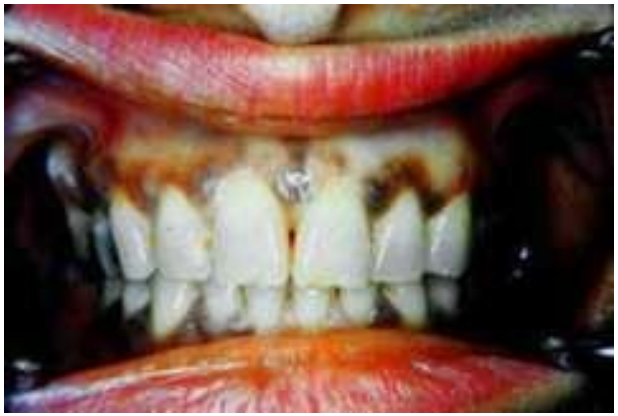


- Hyponatremia is a characteristic biochemical feature in primary adrenal insufficiency and is found in 80% of patients at presentation
- Hyperkalemia is present in 40% of patients at initial diagnosis
- in secondary adrenal insufficiency due to diminished inhibition of ADH by cortisol, resulting in mild syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
- Glucocorticoid deficiency → increased TSH

Acute adrenal insufficiency:

- usually occurs after a prolonged period of nonspecific complaints
- is more frequently observed in patients with primary adrenal insufficiency

1. Postural hypotension may progres
2. Adrenal insufficiency may mimic features of acute abdomen with abdominal tenderness, nausea, vomiting, and fever.
3. In some cases, the primary presentation may resemble neurologic disease, with decreased responsiveness, progressing to stupor and coma.
4. An adrenal crisis can be triggered by an intercurrent illness, surgical or other stress, or increased glucocorticoid inactivation (e.g., hyperthyroidism)

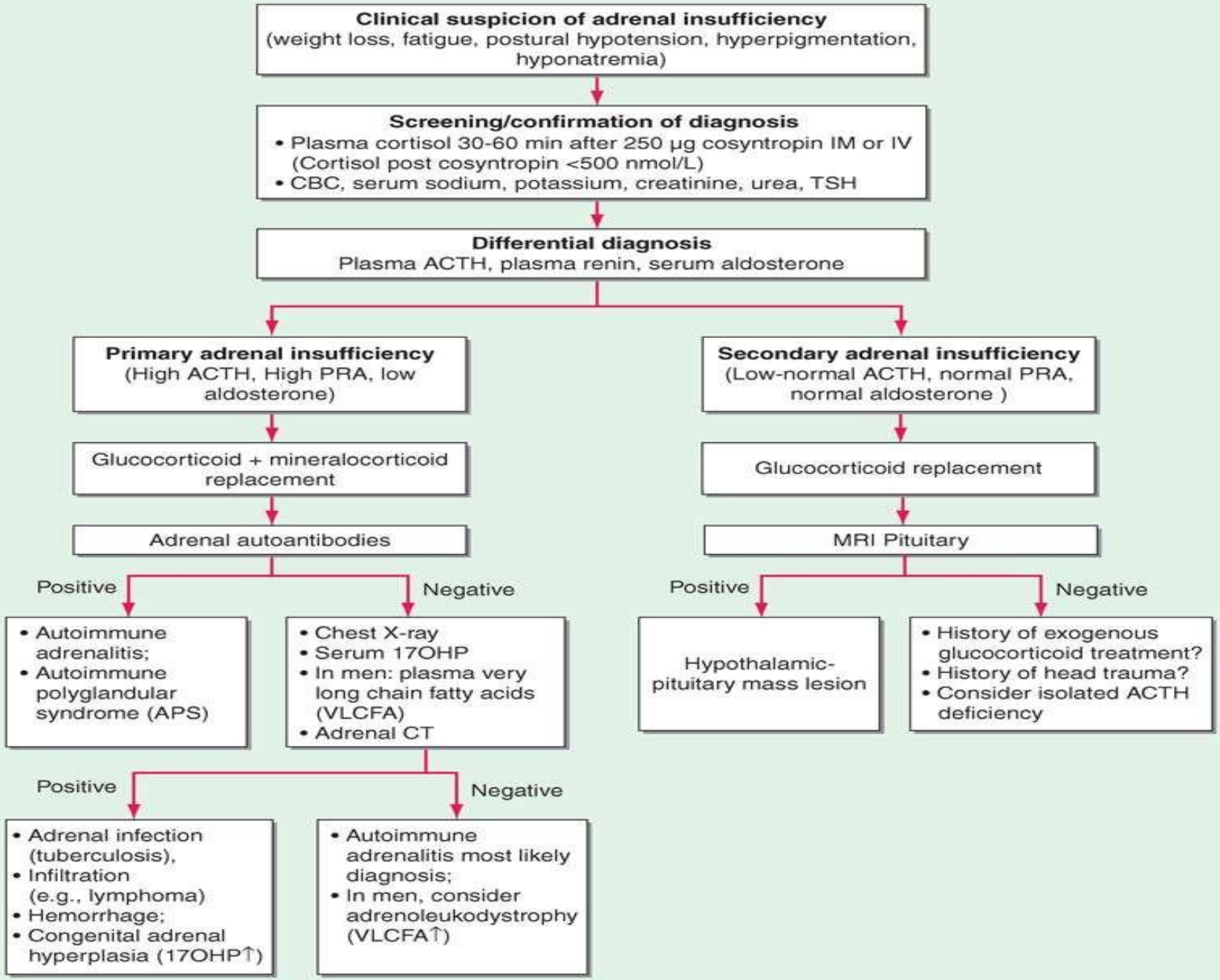
Diagnosis:

- cosyntropin test

a safe and reliable tool with excellent predictive diagnostic value
The cut-off for failure is usually defined at cortisol levels of <500–550 nmol/L (18–20micro g/dL) sampled 30–60 minutes after ACTH stimulation.

- the insulin tolerance test

Algorithm for the Management of the Patient with Suspected Adrenal Insufficiency



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Treatment: Acute Adrenal Insufficiency

1. immediate initiation of rehydration, usually carried out by saline infusion at initial rates of 1 L/h
2. continuous cardiac monitoring
3. Glucocorticoid replacement should be initiated by bolus injection of 100 mg hydrocortisone
4. followed by the administration of 100–200 mg hydrocortisone over 24 h, either by continuous infusion or provided by several IV or IM injections.
5. Mineralocorticoid replacement can be initiated once the daily hydrocortisone dose has been reduced to <50 mg

Treatment: chronic Adrenal Insufficiency

- 15–25 mg hydrocortisone in two to three divided doses
- Pregnancy may require an increase in hydrocortisone dose by 50% during the last trimester
- In all patients, at least one-half of the daily dose should be administered in the morning.
- Long-acting glucocorticoids such as prednisolone or dexamethasone are not preferred

Treatment: isolated primary adrenal insufficiency

- monitoring should include screening for autoimmune thyroid disease
- female patients should be made aware of the possibility of premature ovarian failure
- bone metabolism
- stress-related glucocorticoid dose adjustments
- need for IV hydrocortisone injection at a daily dose of 100 mg in cases of prolonged vomiting, surgery, or trauma
- *Mineralocorticoid replacement* in primary adrenal insufficiency should be initiated at a dose of 100–150 (micro g) fludrocortisone
- serum sodium, potassium, and plasma renin should be measured regularly
- measuring blood pressure, sitting and standing, to detect a postural drop indicative of hypovolemia
- *Adrenal androgen replacement* is an option in patients with lack of energy, despite optimized glucocorticoid and mineralocorticoid replacement


THANKS FOR YOUR ATTENTION