

DISEASES OF ADRENAL GLAND- 2

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PRIMARY HYPERALDOSTERONISM

- Chronic excessive production of aldosterone
- Patients develop hypertension, hypokalemia, suppression of renin-angiotensin system and decreased renin activity
- Primary hyperaldosteronism is caused by one of three diseases:

(1) Bilateral idiopathic hyperaldosteronism (60%):

- Bilateral nodular hyperplasia of zona glomerulosa cells
- Most commonly sporadic, old patients, mild hypertension
- Germline mutation in KCNJ5
- Morphology: diffuse enlargement of the adrenal gland, sometime subtle and not obvious



PRIMARY HYPERALDOSTERONISM

- **(2) Adrenocortical neoplasm (35%):**
 - Functional adenoma or carcinoma
 - Conn syndrome: adrenal adenoma that secretes aldosterone only, more common in middle-age women
 - 50% harbor KCNJ5 mutation, which encodes potassium channel on zona granulosa cells (called GIRK4 protein), mutant protein allows influx of sodium and activation of aldosterone synthase enzyme, other similar mutations affects CACNA1H and ATP1A1 genes
 - Morphology: adenoma is small, more common on left adrenal, buried within the gland (difficult to be seen in radiology), yellow in color and resemble fasciculata cells. Spironolactone bodies: intracellular eosinophilic material following treatment with antihypertensive drugs
 - The other adrenal gland is NOT atrophic



PRIMARY HYPERALDOSTERONISM

- **(3) Familial hyperaldosteronism (5%)**
- Four subtypes
- FH-1 is the most common (AKA glucocorticoid-remediable aldosteronism), mutation in CYP11B2 (encoding aldosterone synthase), becomes sensitive to ACTH
- The other four subtypes are rare



SECONDARY HYPERALDOSTERONISM

- Activation of renin-angiotensin system
- Increased level of plasma renin, occurs in:
- Decreased renal perfusion (renal artery stenosis or arteriolar nephrosclerosis)
- Arterial hypovolemia and edema (congestive heart failure, cirrhosis, nephrotic syndrome)
- Pregnancy (estrogen-induced)



ADRENOGENITAL SYNDROMES

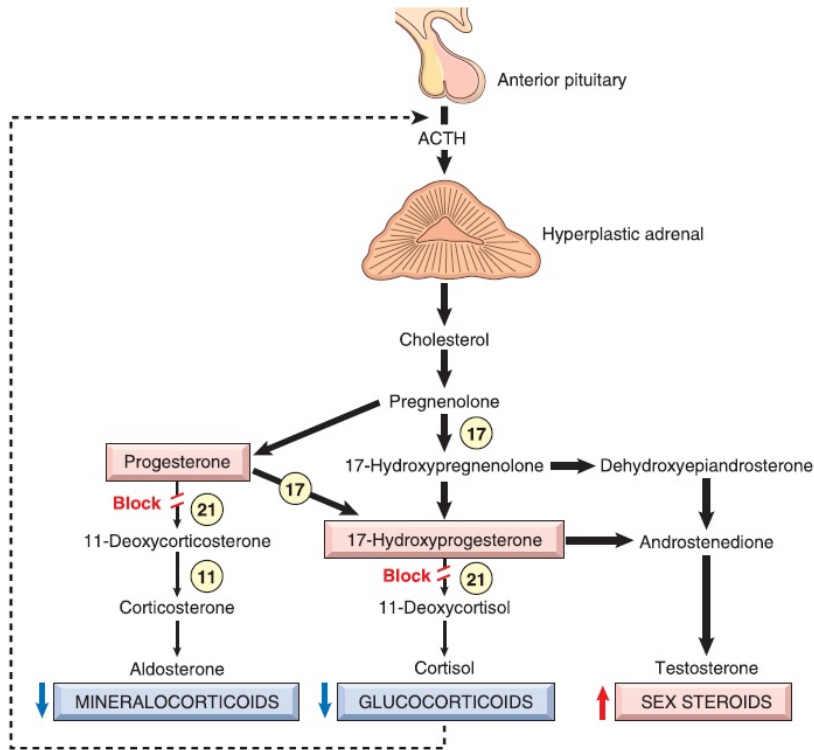
- Adrenal secretes dehydroepiandrosterone and androstenedione which converts to testosterone
- Secretion is ACTH-dependent
- Adrenocortical neoplasm associated with virilization: carcinoma is more common than adenoma, can be pure or mixed with hypercortisolism



CONGENITAL ADRENAL HYPERPLASIA

- Group of autosomal recessive disorders
- Deficiency in enzymes responsible for synthesizing cortisol
- Steroid precursors accumulate and shifts to synthesis of androgens resulting in virilization
- Maybe associated with deficiency in aldosterone synthesis, too
- 21-hydroxylase deficiency: the most common deficiency (90%), mutation in CYP21A1 gene, variable degree of deficiency, results in either:
 - Salt wasting syndrome: associated with deficiency in aldosterone, cortisol and catecholeamine synthesis, appears in utero or shortly after birth (hyponatremia, hypokalemia, hypotension, cardiovascular collapse, virilization in females)
- Simple virilization: no salt wasting, genital ambiguity
- Late-onset adrenal virilism: common, partial enzyme deficiency: hirsutism, acne, irregular menses
- Morphology: bilateral nodular hyperplasia of adrenals, brown, hyperplasia of pituitary corticotroph cells





Consequences of C-21 hydroxylase deficiency. 21-Hydroxylase deficiency impairs the synthesis of both cortisol and aldosterone at different steps (shown as "Block" in the biosynthesis pathway). The resultant decrease in feedback inhibition (*dashed line*) causes increased secretion of adrenocorticotropic hormone, resulting ultimately in adrenal hyperplasia and increased synthesis of testosterone. The sites of action of 11-, 17-, and 21-hydroxylase are shown as numbers in circles.



ADRENOCORTICAL INSUFFICIENCY

- Primary: adrenal failure (acute or chronic)
- Secondary: ACTH deficiency
- Primary acute adrenocortical insufficiency: sudden withdrawal of exogenous steroids, crisis in chronic insufficiency, massive adrenal hemorrhage (newborns, difficult delivery and hypoxia), coagulopathy
- Waterhouse-Friderichsen syndrome: overwhelming bacterial infection (classically occurs in *Neisseria meningitidis*), direct injury to adrenal vessels resulting in hemorrhage and damage to adrenals



PRIMARY CHRONIC ADRENOCORTICAL INSUFFICIENCY

- Called Addison disease
- Uncommon
- Progressive destruction of adrenal cortex
- Symptoms appear after 90% damage to adrenocortical tissue
- Causes: autoimmune inflammation, infections (HIV, TB)



PHEOCHROMOCYTOMA

- Tumor of adrenal medulla (chromaffin cells)
- Secretes catecholamines, results in hypertension
- 10% bilateral, 10% biologically malignant, 10% not associated with hypertension, 10% arises in extra-adrenal sites (carotid body, called paraganglioma), 10% familial (early-life onset)
- Genetic mutations in growth-factor receptor pathway genes (RET, NF1) or increased activity of hypoxia-induced transcription factors (HIF-1 α , HIF-2 α)
- Morphology: variable size, may show necrosis, bleeding, incubation with potassium dichromate produces dark brown color (chromaffin)
- Histology: small nests of cells separated by supporting sustentacular cells (zellballen)
- Malignancy is determined by the presence of metastasis, not histology

