DISEASES OF ADRENAL GLAND

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HYPERCORTISOLISM

- AKA Cushing syndrome
- Can be exogenous (iatrogenic) or endogenous (less common)
- Endogenous causes are divided into ACTH-dependent and independent
- **ACTH-secreting PA** is the most common cause of endogenous hypercortisolism (60%), AKA Cushing Disease, more common in women, young adults, functional microadenoma
- Adrenal glands show bilateral nodular hyperplasia

HYPERCORTISOLISM

- **Ectopic ACTH production:**
- 5-10% of endogenous Cushing syndrome cases
- More common in men, middle age
- Small cell carcinoma of lung, carcinoid tumor, medullary carcinoma of thyroid, pancreatic neuroendocrine tumors
- In some cases, ectopic production of CRH
- Again, bilateral adrenal nodular hyperplasia
- Pathologic changes is less prominent than pituitary cause, secondary to poor prognosis of accompanied cancer

HYPERCORTISOLISM

- **Primary adrenal adenoma**
- 10-20% of ACTH-independent cases
- Low ACTH level (negative feedback on pituitary)
- PRKAR1A genetic mutation
- The other adrenal gland is atrophic
- More common in women
- Adrenal gland is <30 g
- Non-functional adrenal adenoma is more common

HYPERCORTISOLISM

- **Adrenal carcinoma**
- 5-7% of ACTH-independent cases
- Very large size of adrenal glands
- Produces very high level of cortisol
- Genetic mutations in: activation of beta-catenin (CTNNB1), inactivation of TP53, MEN1 and PRKAR1A
- The adrenal gland is > 200 g
- The other adrenal gland is atrophic

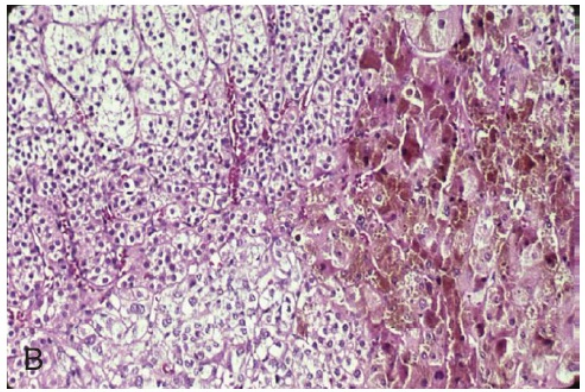
HYPERCORTISOLISM

- Primary adrenal hyperplasia:
- Independent of ACTH
- Rare
- Shows bilateral adrenal cortical hyperplasia, nodules are larger than 1 cm
- Familial disease: inherited mutation in the tumor suppressor gene: armadillo repeat containing 5 (ARMC5)
- Sporadic disease: 50% show ARNC5 mutation, others show ectopic production of G-protein coupled hormone receptors (similar action of ACTH)
- Syndromic disease: McCune Albright syndrome, germline activating mutation in GNAS, produces excessive cAMP multisystemic disease

HYPERCORTISOLISM

- Micronodular bilateral adrenal hyperplasia
- ACTH-independent
- Small nodules (<1 cm)
- Two variants: primary pigmented nodular adrenocortical disease or Carney complex (multisystemic disease of endocrine and non-endocrine neoplasms)
- Both variants harbor mutation in cAMP-dependent protein kinase (PRKAR1A gene), producing excessive cAMP

Diffuse hyperplasia of the adrenal gland contrasted with a normal adrenal gland (top). In cross-section, the hyperplastic adrenal cortex is yellow and thickened, and a subtle nodularity is seen in this gland from a patient with ACTH dependent Cushing syndrome.



(A) Micronodular adrenocortical hyperplasia with prominent pigmented nodules in the adrenal gland. (B) On histologic examination, the nodules are composed of cells containing lipofuscin pigment, seen in the right part of the field.

CLINICAL SYMPTOMS OF CUSHING DISEASE

- Hypertension
- Central obesity, moon face, buffalo hump
- Proximal muscle weakness (atrophy)
- Hyperglycemia, glucoseurea, polyurea, polydipsia
- Bone resorption (osteoporosis)
- Collagen degradation (thin skin, easy bruise, poor wound healing, striation
- Hisrutism
- Menstrual abnormalities
- Immune suppression
- Mental and psychotic disturbances

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
- 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

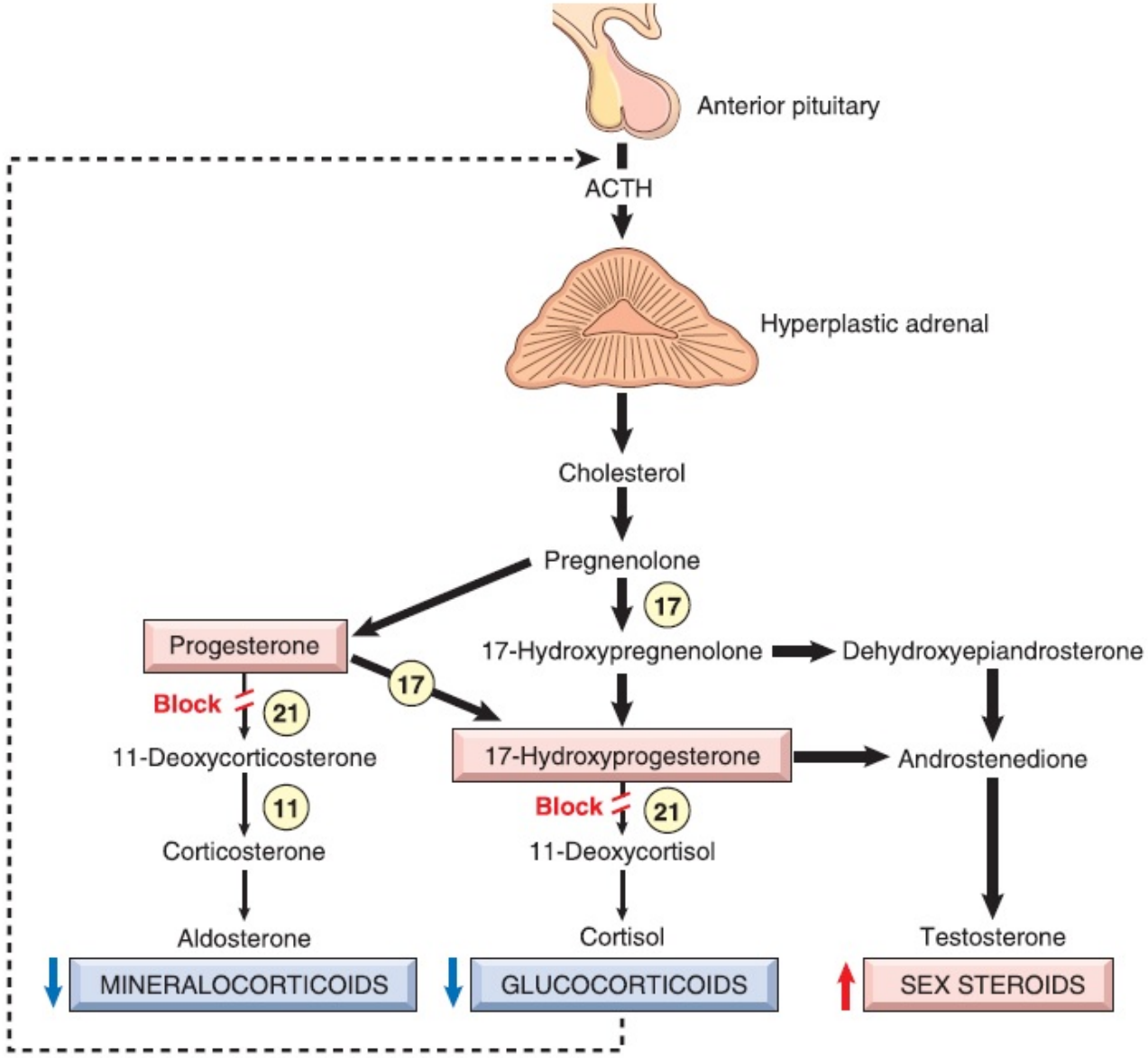
- Activation of renin-angiotensin system
- Increased level of plasma renin, occurs in:
- Decreased renal perfusion (renal artery stenosis or arteriolar nephrosclerosis)
- Arterial hypovolemia and edema (congestive heart failure, cirrhosis, nephrotic syndrome)
- Pregnancy (estrogen-induced)

ADRENOGENITAL SYNDROMES

- Normally, the adrenal glands secrete 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, 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$^{\alpha}$, HIF-2$^{\alpha}$)
- 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