Pathology of the Adrenal Gland
MHD II 2018-19

Today’s Topics

• Brief review of adrenal gland morphology
• Disorders of Adrenal Cortex
• Disorder of Adrenal Medulla
• MEN Syndromes

Adrenal Review

• Paired glands
• Suprarenal location
• ~4-6 grams each

• Cortex derived from Mesoderm
• Medulla neuroectoderm derivation
Diseases of Adrenal Cortex

- Hyperfunction
  - Hypercortisolism
  - Hyperaldosteronism
  - Androgen excess (virilizing, adrenogenital syndromes)
Hypercortisolism (Cushing Syndrome)

- Elevated Glucocorticoid levels

Pituitary Cushing Syndrome

- 70% of endogenous Cusings
- Young adulthood; Women 4x > men

  - Sometimes hypothalamic CRH-producing tumor leads to Corticotroph cell hyperplasia

  - Adrenal cortex with nodular hyperplasia
    - ACTH Dependent Cushings

Ectopic ACTH Secretion (paraneoplastic)

- 10% cases Cushing
- Non-pituitary tumors secrete ACTH
  - Most common?
- Adrenals → bilateral cortical hyperplasia
  - ACTH dependent Cushings
Primary Adrenal Neoplasms

• Adrenal ADENOMA
• Adrenal CARCINOMA
• Primary cortical HYPERPLASIA

• 15-20% of endogenous Cushing

• ACTH Independent Cushing
  • Adrenals function autonomously

Adrenal Gland Morphology

Robbins Basic Pathology, 10th edition, p 786

Adrenal Gland Morphology

Robbins Basic Pathology, 10th edition, p 787
Typical findings in Cushing syndrome

Robbins Basic Pathology, 10th Edition

Diagnostic evaluation for suspected Cushing syndrome. Initial tests (1-mg overnight dexamethasone suppression test, or 24-hour urine cortisol, or midnight salivary cortisol level) will confirm or exclude hypercortisolism. Then, the plasma ACTH level will differentiate adrenal (ACTH-independent) from ACTH-dependent causes. In the case of elevated or normal ACTH levels, localization by inferior petrosal sinus sampling will identify or exclude a pituitary origin. Boxes enclose clinical diagnoses, and ovals indicate diagnostic tests.

Ectopic ACTH Cushing Disease
Dexamethasone Suppression Test

- Administer Dexamethasone at 11pm
  - Normal → early morning surge in cortisol suppressed
  - Cushing Syndrome → Cortisol secretion not, or not as greatly, suppressed

Hyperadrenalism - Primary

Hypertension

Essential HTN = idiopathic
- 90% of HTN cases
  - "Nodular Hyperplasia"
    - Nodules
    - Hypertensive changes
      - Nodules
    - Hypertension

Primary Hyperadrenalism

- Mutations of KCNJ5 gene
  - Encodes potassium channel protein
  - Expressed in adrenal gland
Primary Hyperaldosteronism

Secondary hypertension, hypokalemia, metabolic alkalosis

Suppression of renin-angiotensin system → decreased plasma renin activity

Adrenaline

Excess aldosterone leads to hypertension
Aldosterone results in hypokalemia and hyperaldosteronism
Excess potassium excretion leads to hyperaldosteronism
Volume expansion may be clinically absent due to "diuretic escape"

Renal - loss of H⁺ into the urine

- Metabolic alkalosis mimics hyperaldosteronism
- Volume expansion/hypovolemia

Primary Hyperaldosteronism

- Management
  - Adenoma (Conn Syndrome)
    - Surgical Resection of tumor
  - Hyperplasia
    - Aldosterone receptor inhibitors
      - Drug of choice: __________________
      - Side effects: __________________
    - Other option: eplerenone

Secondary Hyperaldosteronism

- Aldosterone release in response to activation of renin-angiotensin system
  - Decreased renal perfusion
    - Nephroclerosis, renal artery stenosis
  - Arterial hypovolemia
    - CHF, cirrhosis, nephrotic syndrome
  - Pregnancy
    - Estrogen-induced increased in plasma renin substrate
Adrenogenital Syndromes

- Definition:
  - Group of disorders caused by androgen excess

- Etiologies
  - Primary gonadal disorders
  - Primary adrenal disorder
  - Adrenocortical neoplasm
  - Congenital adrenal hyperplasia

FHB Return

- Adrenal Cortex
  - Produces adrenal androgens: DHEA (dehydroepiandrosterone)
    - Precursor for the more potent androgen testosterone, and for estrogens
    - Converted to testosterone in peripheral tissues
    - "Weak androgen" due to its low binding affinity for androgen receptors
    - Adrenal androgen production regulated by ACTH

“Virilizing” Adrenocortical Neoplasm

- Carcinoma more often than adenoma
Congenital Adrenal Hyperplasia (CAH)

- Autosomal recessive disorders
- Characterized by hereditary defect in enzyme involved in adrenal biosynthesis, particularly cortisol
  - Decreased cortisol → increased ACTH secretion (loss of feedback inhibition)
  - → adrenal hyperplasia → increased production of cortisol precursor proteins → channeled into synthesis of androgens → virilization
  - Depending on the enzyme defect, aldosterone secretion may be impaired

CAH

- Most common enzyme defect
  - 21-hydroxylase deficiency
    - Total lack to mild loss
Alterations in steroid hormone synthesis: Deficiency of 21-hydroxylase accounts for 95% of genetic abnormalities in adrenal steroid hormone synthesis. This enzyme converts progesterone to deoxycorticosterone and 17-hydroxyprogesterone to 11-deoxycortisol. Thus, more pregnenolone is shunted to the DHEA-androstenedione pathway (more androgen synthesis), resulting in virilization (presence of masculine traits). In addition, aldosterone deficiency leads to sodium wasting.

### 21-Hydroxylase Deficiency

**Excess androgen activity**
- Masculinization in females
  - Infants
    - Clitoral hypertrophy
    - Phallic enlargement
  - Postpubertal
    - Gynecomastia
    - Acne
    - Hirsutism
- Males
  - External genitalia enlargement
  - Precocious puberty
  - Oligospermia

**Aldosterone deficiency**
- Salt wasting

**Cortisol deficiency**
- Risk of acute adrenal insufficiency

**Treatment**
- Glucocorticoids: Tx for cortisol deficiency, decreased ACTH: decrease excessive secretion of steroid hormones.
- Mineralocorticoids: # aldosterone deficiency

### Homework:

- Determine manifestations of 11-Hydroxylase deficiency
  - 2nd most common enzyme deficiency of CAH
Diseases of Adrenal Cortex

- Hypofunction
  - Primary hypoadrenalism
  - Secondary hypoadrenalism (ACTH deficiency)

Primary Adrenal Insufficiency (Addison Disease)

- Destruction or dysfunction of adrenal cortex
  - Etiologies
    - Autoimmune (~60-80% in developing countries)
    - Infections
      - Tuberculosis
      - AIDS
    - Fungal
    - Hemochromatosis
    - Sarcoidosis
    - Amyloidosis
    - Metastases
    - Waterhouse Friderichsen Syndrome

A closer look at some etiologies

- Autoimmune adrenalitis
  - Autoimmune destruction of steroid producing cells
  - Autoantibodies to several key steroidogenic enzymes

- Adrenal morphology
  - Shrunken glands
  - Lymphoid infiltrate in cortex
• Infections
  • TB – overall less common with improved anti-TB therapy
    • Some resurgence with HIV infection and immunodeficiency
    • Usually active infection in other sites (lungs, GU tract)
  • Fungi
    • Disseminated Histoplasma capsulatum, Coccidioides immitis
  • AIDS
    • Often due to complications of immunodeficiency
      • Other infections (CMV, MAI)
      • Kaposi sarcoma

• Metastatic neoplasms
  • May destroy enough adrenal cortex to produce insufficiency
    • Carcinomas
      • Lung, breast include most common primary sites

• Waterhouse-Friderichsen Syndrome
  • Massive adrenal hemorrhage
  • Sepsis
    • Classic association with which infectious agent?
      • More common in children
      • Less common with other infections
  • Pathogenesis?
    • Direct bacterial seeding of small vessels in adrenal
    • DIC
    • Endotoxin-induced vasculitis
    • Hypersensitivity vasculitis
Waterhouse-Friderichsen Syndrome

Adrenal glands black-red from extensive hemorrhage

Marked hemorrhagic necrosis

Source of images: Utah Web Path

Secondary Adrenal Insufficiency

- Disorder of hypothalamus or pituitary → reduces output of ACTH
  - Infection, infarction, tumor, irradiation
- Adrenals are markedly atrophic

Source: Disorders of the Adrenal Cortex, Pathophysiology of Disease: An Introduction to Clinical Medicine, 7e
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Signs and Symptoms

Glucocorticoid Deficiency
• Fatigue, weakness
• Weight loss, anorexia
• Myalgia, joint pain
• Fever
• Hypoglycemia
• Low BP, postural hypotension
• Hyponatremia (due to loss of inhibition of AVP release)

Mineralocorticoid Deficiency (Primary Adrenal Insufficiency only)
• Hyponatremia
• Hyperkalemia
• Low BP, postural hypotension
• Abdominal pain nausea, vomiting
• Increased serum creatinine (volume depletion)
• Salt craving

Melanocyte stimulating hormone
Aldosterone deficiency
Aldosterone secretion usually preserved

Mineralocorticoid deficiency
Primary adrenal insufficiency
Addison disease
Aldosterone deficiency
Aldosterone secretion usually preserved

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Acute Adrenal Crisis

- Intractable vomiting, abdominal pain, hypotension, coma, cardiovascular collapse
- Death unless corticosteroids replaced immediately
- Causes?
  - Chronic adrenal insufficiency with acute physiologic stress without appropriate increase in steroid dose
  - Rapid withdrawal of exogenous corticosteroids

Diagnostic evaluation for suspected adrenal insufficiency. The first step is to perform a rapid ACTH stimulation test to ascertain whether there is adrenal insufficiency. Then, the plasma ACTH level differentiates between primary and secondary adrenal insufficiency. In cases where the serum cortisol after ACTH stimulation is normal, but there is a high suspicion of adrenal insufficiency or where it may be of recent onset (e.g., with pituitary apoplexy), an insulin tolerance test is conducted. Alternatively, a measurement of DHEAS, which is dependent on the action of ACTH, or a metyrapone test can be helpful. Boxes enclose clinical diagnoses, and ovals indicate diagnostic tests.
Adrenal Medulla
- Neural crest derivation
- Populated by chromaffin cells and their supporting sustentacular cells
- Secrete catecholamines
- Similar collections of cells distributed throughout the body in the extraadrenal paraganglion system
- Primary Disease Process – Neoplasms
  - Pheochromocytoma
  - Neuroblastoma

Pheochromocytoma
- Neoplasm arising from neuroendocrine cells (chromaffin cells) in the paraganglion system (adrenal medulla/extra-adrenal paraganglion system)
  - Secrete norepinephrine > epinephrine
  - Give rise to potentially surgically correctable form of hypertension
  - Increased total peripheral resistance
  - 10% rule

Pheochromocytoma 10% Rule
- 10% extraadrenal like organs of Zuckerkandl and carotid body (called paragangliomas)
- 10% bilateral
- 10% malignant
- 25% familial (change in the 10% rule) being associated with germline mutation in six known genes
  1. RET gene (MEN II and III)
  2. NF1 (type 1 neurofibromatosis)
  3. VHL (Von Hippel–Lindau)
  4. Genes SDHB, SDHC, and SDHD with succinate dehydrogenase complex involved in mitochondrial oxidative phosphorylation
Clinical

- Hypertension - sustained or in paroxysms
- Headache, sweating, anxiety, tremor
- Symptoms/signs caused by release of catecholamines can precipitate an AMI, CHF, ventricular fibrillation, CVA
- Chemical diagnosis; elevation of urinary catecholamine metabolites including metanephrine and vanillylmandelic acid (VMA)
Clinical Aspects

- Beta blockers should not be administered until α blockade established
  - Blockade of β2-adrenergic receptors (promote vasodilatation), will allow unopposed α adrenergic receptor activation → marked vaso-constriction and hypertension

Neuroblastoma

- A neoplasm which arises in the adrenal medulla or extra-adrenal paraganglion tissue.
- One of most common childhood neoplasms
  - 90% occur before age 5 years
    - Large abdominal mass in a child <2 years with fever
    - Older child presents with metastases
  - Tumors may produce catecholamine precursors:
    - Vanillylmandelic acid (VMA) and homovanillic acid (HVA) in small amounts

Neuroblastoma

Pathology

- Macroscopic: large bulky tumors
  - 25% in adrenal glands
  - Others arise in the paravertebral regions of the posterior mediastinum and abdomen
- Microscopic: small, primitive appearing cells with dark nuclei; sheets or rosettes
  - “Small round blue cell tumor”
Multiple Endocrine Neoplasia (MEN)

- Inherited diseases with lesions (hyperplasia, adenomas and carcinomas) of multiple endocrine organs
- Endocrine tumors associated with MEN
  1. Occur at younger age
  2. Multiple endocrine organs involved; synchronous/metachronous
  3. Multifocal tumors
  4. May be preceded by asymptomatic stage of endocrine hyperplasia
  5. More aggressive and recur

Memorization Time
MEN 1
• Autosomal dominant
• MEN1 gene (11p13) is tumor suppressor gene
• 3Ps – Parathyroid, Pancreas and Pituitary
  • Primary hyperparathyroidism most common manifestation
  • Hyperplasia or adenoma
  • Endocrine tumors of Pancreas
  • Leading cause of death patients – functional tumors, metastases
  • Pituitary most commonly has prolactin secreting macroadenomas

MEN 2A
• Autosomal dominant
• Mutations in the Ret protooncogene (10q 11.2)
  1. Thyroid
     • Medullary carcinoma in virtually all untreated cases, in first 2 decades, may be multiple
  2. Adrenal Medulla
     • Pheochromocytomas in 50% of patients, only 10% are malignant
  3. Parathyroid – 10-20% have hyperparathyroidism

MEN 2B
• Spectrum of thyroid and adrenal medullary changes similar to 2A
• Differences:
  1. Mucosal ganglioneuromas and marfanoid habitus characteristic
  2. Parathyroid manifestations absent
• Relatives of MEN2 kindred are counseled to get genetic testing ➔ if harbor Ret mutations, advised to undergo prophylactic thyroidectomy to prevent development of medullary carcinomas
A 50-year-old man has episodic headaches for 3 months. On physical examination his blood pressure is 185/110 mm Hg, with no other remarkable findings. Laboratory studies show sodium 145 mmol/L, potassium 4.3 mmol/L, chloride 103 mmol/L, CO2 26 mmol/L, glucose 91 mg/dL, and creatinine 1.3 mg/dL. Abdominal CT scan shows a 7 cm left adrenal mass. During surgery, as the left adrenal gland is removed, there is a marked rise in blood pressure. Which of the following laboratory test findings most likely explains his findings?

A. Decreased serum cortisol
B. Decreased urinary homovanillic acid
C. Increased serum ACTH
D. Increased urinary free catecholamines
E. Elevated serum ANCA

A 45-year-old man has a 4 month history of nonfocal, generalized headaches. On physical examination he is found to have a blood pressure of 170/110 mm Hg. Laboratory studies show a serum sodium of 146 mmol/L, potassium 2.3 mmol/L, chloride 103 mmol/L, CO2 27 mmol/L, glucose 82 mg/dL, and creatinine 1.2 mg/dL. His plasma renin activity is 0.1 ng/mL/hr and his serum aldosterone 65 ng/mL. Which of the following is the most likely cause for his findings?

A. 21-hydroxylase enzyme deficiency
B. Adrenal cortical adenoma
C. Pituitary adenoma
D. Exogenous corticosteroid administration
E. Renal cell carcinoma
A 45-year-old woman with severe rheumatoid arthritis has been on chronic corticosteroid therapy for the past 15 years. She is admitted for an orthopedic procedure to correct joint deformity from her disease. She continues to receive her regular dosage of 5 mg of prednisone per day. Three days postoperatively, she develops an aspiration pneumonia with *Klebsiella pneumoniae* cultured from sputum. Five days following the surgery, she becomes obtunded. Laboratory findings at that time include: sodium 105 mmol/L, potassium 5.4 mmol/L, chloride 87 mmol/L, CO₂ 16 mmol/L, glucose 40 mg/dL, and creatinine 1.1 mg/dL. Which of the following complications is most likely to have occurred in this patient?

A. Anterior pituitary necrosis  
B. Waterhouse-Friderichsen syndrome  
C. Acute Addisonian crisis  
D. Conn syndrome  
E. 21-hydroxylase deficiency