Disorders of the adrenal cortex

Timea Baló MD.
Semmelweis University
III. Dept of Internal Medicine
Contents

- Anatomy of the adrenal glands
- Biochemistry and physiology
- Basic principles in the laboratory evaluation of adrenocortical function
- Hyperfunction of the adrenal cortex
- Clinical presentation and evaluation of adrenocortical tumors
Anatomy
Anatomy of the adrenal glands
The Suprarenal (Adrenal) Glands

- Paired retroperitoneal pyramidal organs on the superior surface of the kidneys – highly vascularized

- 3 groups of 60 small suprarenal arteries supply each gland
  - the superior suprarenal arteries from the inferior phrenic artery
  - middle suprarenal arteries from the aorta;
  - inferior suprarenal arteries from the renal artery

- Veins
  - left suprarenal vein drains into the renal vein and the right suprarenal vein drains into the inferior vena cava
Anatomy and Histological Organization of the Suprarenal Gland
Biosynthesis of adrenal steroid hormones
Mineralocorticoid synthesis

ADRENAL CORTEX

Cholesterol → P450scc → Pregnenolone

3βHSD → Progesterone → P45017α → 17α-OH Pregnenolone

3βHSD → 17α-OH Progesterone → P45017α → DHEA

P450c21 → Deoxycorticosterone

P450aldo → Corticosterone

P450aldo → 18-O-Corticoesterone

P450aldo → Aldosterone

P450c21 → Deoxycortisol → P450c11 → Cortisol

17βHSD → Testosterone → Estradiol

Androstenedione → Estrone

GONADS
Zona glomerulosa-function

- The cells secrete **mineralcorticoids**, mainly aldosterone
- It’s essential for life
- The main regulator is the kidney, via the renin-angiotensin-aldosterone system
- The EC K+ elevation impoves aldosterone production
- Promotes sodium and water retention and potassium elimination by the kidney
- Expands ECF volume
Glucocorticoid synthesis
Zona fasciculata function

- Cells secrete **glucocorticoids** (important in lipid, protein and carbohydrate metabolism)
- Cortisol improves glucose production from amino acids and fatty acids
- Inhibits the cells glucose uptake and consumption
- Secretion is regulated by ACTH
- The daily secretion of cortisol ranges between 40 and 80 umol (15-30 mg) with a pronounced circadian cycle.
- Free cortisol, protein bound cortisol, and cortisol metabolites
Steroid transport

- Free cortisol is active
- Normally less than 5% of circulating cortisol is free.
- Unbound cortisol and its metabolites are filterable at the glomerulus.
- Increased quantities of free steroid are excreted in the urine in states characterized by hypersecretion of cortisol.
- Plasma has 2 cortizol binding system
- CBG binding is reduced in areas of inflammation, thus increases the local concentration of free cortisol
- When the concentration of cortisol is >700 nmol/l (25 ug/dl) part of the excess binds to albumin, and a greater proportion than usual circulates unbound.
Androgen synthesis
The major androgen secreted by the adrenal is dehydroepiandrosterone (DHEA) and its sulfuric acid ester (DHEAS).

They are transformed to testosterone and it’s biologically active.

Approximately 15-30 mg of these compounds is secreted daily.

Smaller amounts of androstendion, 11-β-OH androstendione and testosterone are secreted.

DHEA is the major precursor of urinary 17-ketosteroids.
Androgen production of the adrenals

- The androgen production of the adrenals are characterized with big variability depending upon age.
- Fetal adrenal cortex produces a lot of DHEA and DHEAS, after birth it decreases, before puberty increases again: ADRENARCHE.
- In males they play role in emergence of secondary sex characteristics.
- In females they inhibit the sex hormone production (they aren’t produced until menopause).
Regulation: HPA axis

- ACTH is processed from a large precursor molecule (POMC)
- POMC is made in a variety of tissues (brain, anterior and post pituitary and lymphocytes)
- ACTH is synthesized and stored in basophilic cells of the anterior pituitary
- Release of ACTH is stimulated by CRH
Basic principles in the laboratory evaluation of adrenocortical function
The end products of steroid biosynthesis: morning concentrations

- Aldosterone
- Cortisol
- Dehydroepiandrosterone-sulphate
- Androstendione

Indication:

- Hormonal evaluation of an adrenal tumor
- HPA function disturbances
- Diff. diagnosis of hypertension, obesity, hyperandrogenism
Patient as a source of imprecision

Physiological states which influence hormone assays

- age
- pregnancy
- menstruation cycle (LH, FSH, E2, P ...)
- nutrition
- daily rythm of hormones (eg. cortisol, PRL...)
- stress (eg. renin activity, catecholamines)
- sleep-wake cycle
Hyperfunction of the adrenal cortex

- Excess cortisol: Cushing’s syndrome
- Excess aldosterone: Hyperaldosteronism (Conn’s syndrome)
- Excess adrenal androgens: Adrenal virilism

These syndromes do not always occur in pure form but may have overlapping features
Cushing’s syndrome

Harvey Cushing
Normal pattern of ACTH and cortisol production

- Pulzatile secretion
- Cirkadian rythm
Classification

**ACTH dependent**
- Pituitary adenoma (Cushing disease)
- Hypothalamic CRH overproduction
- Ectopic ACTH/CRH syndrome

**ACTH independent**
- Adrenal tumor
  - Adenoma
  - Carcinoma (bimodal age peak, 1-5 yrs & 5-7. decade)
- Bilateral adrenal hyperplasia
- PPNAD (primary pigmented nodular adrenocortical disease)
- AIMAH (macronodular hyperplasia)
- McCune Albright syndrome
- Ectopic adrenocortical adenoma

**Iatrogenic Cushing syndrome**
Clinical symptoms of Cushing’s

<table>
<thead>
<tr>
<th>Usually slow progression, it can be cyclic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Obesity</td>
</tr>
<tr>
<td>• Moon face</td>
</tr>
<tr>
<td>• Thin, easy bruising skin, purplish, striae, acne, hirsutism</td>
</tr>
<tr>
<td>• polyglobulia</td>
</tr>
<tr>
<td>• Proximal muscle weakness, muscle atrophy</td>
</tr>
<tr>
<td>• osteoporosis, fractures (growth failure in children)</td>
</tr>
<tr>
<td>• Hypokalemia, alkalosis</td>
</tr>
<tr>
<td>• hypertension, diabetes mellitus, lipid metabolism disorders</td>
</tr>
<tr>
<td>• Menstrual irregularities, amenorrhoea, infertility</td>
</tr>
<tr>
<td>• Infektion-risk</td>
</tr>
<tr>
<td>• depression</td>
</tr>
</tbody>
</table>
Signs and symptoms
Skeletal problems

- Weakness, proximal muscle atrophy (climbing stairs arm-chair lineup)
- Hypokalemia (increased mineralocortic activity) improves muscle-weakness
- **Bone-loss – osteoporosis:**
  - Compression fractures of vertebrae (20%)
  - Pathologic fractures of ribs and long bones
  - Osteonecrosis of head of the femur (aseptic necrosis)
- Low back pain
- Increased bone resorption leads to hypercalciuria and nephrolithiasis
Diagnosis of Cushing’s syndrome

Hormone tests

1. Prove hypercortisolism
   - Urine **cortisol (min 2x)**
     - low dose dexamethasone test (1 mg)
     - diurnal rhythm of plasma cortisol
     - midnight salivary cortisol (min 2x)

2. Diagnosis the forms of Cushing’s syndrome
   - plasma ACTH
   - high dose dexamethasone test
   - CRH test (vasopressin, desmopressin, metyrapone test)
   - Sinus petrosus inferior samples
   - Imaging techniques (sella MRI, adrenal CT (localisation the source of ectopic overproduction))
Primary hyperaldosteronism

- Primary overproduction of aldosterone
- Suppressed PRA
- Hypertension
- 50% low potassium level
Primary aldosteronism - causes

Unilateral adenoma (small, may occur on either side) **APA**

Bilateral cortical nodular hyperplasia = idiopathic hyperaldosteronism (the cause is unknown) **IHA**

Adrenal carcinoma - rarely
Conn - syndrome

Prof. Jerome W. Conn (1907-1981)
Primary aldosteronism

- Twice as common in women as in men
- Usually occurs between ages of 30 and 50
- Is present in 1% of unselected hypertensive patients
- However the prevalence may be even 5%, it’s depending upon the study population
- In many patients with clinical and biochemical features of primary aldosteronism, a solitary adenoma is not found at surgery
Signs and symptoms

- Progressive depletion of potassium, development of hypokalemia
- Diastolic hypertension, headaches
- Hypertension is due to the increased sodium reabsorption and extracellular volume expansion
The frequency of hypertension in Hungary

<table>
<thead>
<tr>
<th>Sex</th>
<th>Unrecognized</th>
<th>Treated, not controlled</th>
<th>Well controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>41%</td>
<td>29%</td>
<td>30%</td>
</tr>
<tr>
<td>Females</td>
<td>60%</td>
<td>19%</td>
<td>21%</td>
</tr>
</tbody>
</table>
Signs and symptoms

- EKG, X-ray: left ventricular enlargement

- EKG (low potassium): prominent U waves, cardiac arrhythmias, premature contractions

- In the absence of associated congestive heart failure, renal disease or preexisting abnormalities (thrombophlebitis) edema is absent
Complications

- Structural damage to the cerebral circulation, retinal vasculature and kidney
- Proteinuria may occur in 50% of patients
- Renal failure occurs in up to 15%
- Probably excess aldosterone production induces cardiovascular damage independent of its effect on blood pressure
When to screen aldosteronism?

- Hypertension and hypokalemia
- Hypertension and adrenal tumor
- Resistant hypertension (20% incidence)
- Onset of hypertension < 20 years of age
- Severe hypertension ( > 160/100 Hgmm)
- Whenever considering secondary hypertension
Diagnosis

- Case finding strategies
- Confirmatory tests
- Subtype evaluation tests
Screening

- Plasma aldosterone concentration (PAC) and plasma renin activity (PRA)
- Drawn from ambulant seated patient
- Morning blood draw
- Potassium must be normalized (not hypokalemic) to avoid false suppression of aldosterone
Positive screening, further investigation for PHA

- Aldosterone-renin ratio (ARR) > 30
  20-60? PRA is normalized to 0.5 if < 0.5

- AND:
  Aldosterone level >15 ng/dl
Aldosterone suppression tests

- ARR with lack of suppression (Kaplan NM. J Hypertension 22:863-69, 2004)

- **Iv saline suppression**
  500 ml 0.9% Nacl/h for 4 hours
  Draw PAC at time 0’- 240 ‘for short test
  Suppression if PAC <8.5 ng/dl (>10 PA)

- **Oral sodium chloride suppression**
  10 g Nacl daily for 4 days
  On day 4 collect 24 h urine aldosterone, sodium
  Suppression, if aldosterone <14 mcg and sodium >200 mEq/24h

- **Fludrocortisone suppression test**
  High salt diet, and large doses of Astonin H over 4 day hospitalization
Drugs influencing tests

- **ARR can’t be assessed:**
  - spironolacton, eplerenon
  - amilorid

- **ARR false positive:**
  - Béta blockers, alfa-metildopa
  - clonidin, NSAIDs

- **ARR false negative:**
  - ACE – gátlók, AII receptorblockers
  - nem kálium spóroló diuretikumok
  - dihidropiridin kalcium csatorna blokkolók
  - ösztrogének
Localization

- Abdominal CT scan (thin cuts of adrenal gland), MRI, 131-I-Iodocholesterol
- If the CT scan is negative percutaneous transfemoral bilateral adrenal vein catheterization with adrenal vein sampling (2-3fold increase in plasma aldosterone concentration on the involved side)
- In cases of hyperaldosteronism secondary to cortical nodular hyperplasia no lateralization is found
Adrenal vein sampling

- Best method to detect lateralization
- Adrenal vein/inferior vena cava cortisol ratio must be >2
- Lateralization exists if Aldo/cortisol ratio is 4-fold higher than in contralateral adrenal vein
- Adrenal vein catheterization may help avoid unnecessary surgery and identify microadenomas not detected by CT scan.
Why is Primary Aldosteronism Important?

- Primary aldosteronism may be one of the most frequent causes of secondary hypertension.
- Hypertension can be cured or successfully treated with mineralocorticoid antagonists.
- Aldosterone can cause vascular and cardiac damage independent from hypertension.
Genetic considerations

Glucocorticoid diseases – Congenital adrenal hyperplasia (CAH)

It is the consequence of recessive mutations that cause one of several distinct enzymatic defects

A block in cortisol synthesis may result in the enhanced secretion of adrenal androgens and/or mineralocorticoids depending on the site of enzyme block

In severe congenital virilizing hyperplasia, the adrenal output of cortisol may be so compromised as to cause adrenal deficiency despite of adrenal hyperplasia
CAH

- Most common adrenal disorder of infancy and childhood

- Partial enzyme deficiencies can be expressed after adolescence, predominantly in women with hirsutism and oligomenorrhoea but minimal virilization

- Late onset CAH may account for 5-25% of cases of hirsutism and oligomenorrhoea in women
Types of CAH

1. 21-OH ase deficiency (>90%)
   - Classical – salt wasting (75%; 1:15000)
     - simple virilizing (25%; 1:60000)
   - Nonclassic (1:1000)

2. Others:
   - 11 – hydroxylase deficiency (3-5%, 1:100000)
   - 17 – alpha-hydroxylase /C17 lyase def (1%)
   - 3-beta – OH-steroid –dehydrogenase def (1%)
Pathogenesis of CAH (CYP21A2)

Normal pathway of adrenal steroid synthesis

- Progesterone → 17-hydroxyprogesterone → Adrenal androgens
  - 21-hydroxylase
  - Deoxycorticosterone → 11-deoxycortisol
  - Cortisosterone → Cortisol
  - 18-hydroxyprogesterone → Aldosterone

21-hydroxylase deficiency (absolute)

- Progesterone → 17-hydroxyprogesterone → Adrenal androgens
CAH due to 21-OH deficiency

<table>
<thead>
<tr>
<th></th>
<th>Classic salt wasting</th>
<th>Classic simple virilizing</th>
<th>Nonclassic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>Age at dx</td>
<td>Birth-6mo</td>
<td>Birth-1mo</td>
<td>2-4 yr</td>
</tr>
<tr>
<td>External genitalia</td>
<td>Normal</td>
<td>Ambiguous</td>
<td>Normal</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Low</td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Low</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>17-OHP</td>
<td>Basal&gt;20,000 ng/dL</td>
<td>Basal&gt; 10,000 – 20,000 ng/dL</td>
<td>ACTH stimulated 1,500 – 10,000 ng/dL</td>
</tr>
<tr>
<td>% of normal 21-OH activity</td>
<td>0</td>
<td>1-2</td>
<td>20-50</td>
</tr>
</tbody>
</table>

Diagnosis of 21- hydroxylase deficiency

Suspect a newborn with:

- Genital ambiguity
- Salt-wasting
- Hypotension
- Hypoglycaemia
- Hyponatremia
- Hyperkalemia
- Raised plasma renin activity
In later life…

- PCOS like phenotype
- Adrenal androgen excess (DHEAS, Androstendion)
- Suppressed following glucocorticoid administration

Elevated 17-OH progesterone

- Basal
- After synacthen stimulation in heterozygous cases
Therapy

- Daily administration of glucocorticoids to suppress pituitary ACTH secretion

- In children skeletal growth and maturation must be controlled closely, because overtreatment with glucocorticoid replacement therapy retards linear growth
Clinical presentation and evaluation of adrenal tumors
Evaluation of adrenal masses

- 10-20% of subjects at autopsy have adrenocortical adenomas
- 90% of incidentalomas are nonfunctioning
- If an extraadrenal malignancy is present, there is a 30-50% chance that the adrenal tumor is metastasis
- In the absence of a known malignancy the next step is unclear
- The probability of adrenal cancer is <0.01%
Features of malignant masses

- Large size ( >4-6 cm)
- Irregular margins, and inhomogeneity
- Soft tissue calcifications visible on CT
- Finding characteristic of malignancy on a chemical-shift MRI
- Fine needle aspiration is not useful in diagnosis
- Despite operative intervention most patients with adrenal cancer die within 3 years of diagnosis
- Principal drug for the treatment is mitotane - an isomer of the insecticide DDT
Evaluation of adrenal tumors

Adrenal mass detected on CT scan or on abdominal ultrasound

What is the size/greatest diameter of the lesion?

- < 3 cm
  - Patient has no symptoms and screening laboratory results are normal
    - yes
      - Radiographic surveillance at 3 month, then every 6 month for 2 years
    - no
      - MRI and additional endocrine evaluation
      - yes
        - Referral based on symptoms and laboratory test results
      - no
        - Surgical removal
- > 3 cm, < 6 cm
- > 6 cm
Evaluation of adrenal tumors II.

Adrenal mass

History and physical examination

Clinical suspicion

Cushing's syndrome
- Serum cortisol
- Urinary cortisol (optional)
- ACTH
- 1mg dexamethasone suppression test

Pheochromocytoma
- Should always be evaluated
- Plasma-free metanephrines (best)
- 24h urine for catecholamines/metanephrines

Hyperaldosteronism
- Serum potassium
- Serum aldosterone levels
- Aldosterone-to-renin ratio

Source: Cancer Control © 2002 H. Lee Moffitt Cancer Center and Research Institute, Inc.
Hypodense adrenal adenoma

Abdominal CT showing a 1.5-cm round hypodense left adrenal cortical adenoma (arrow).

Courtesy of William F Young, Jr, MD.
Contrast-enhanced CT scan through the abdomen of a 56-year-old man reveals a complex solid and cystic, calcified mass (arrow) in the right suprarenal fossa extending into the adjacent liver. The tumor proved at surgery to be a carcinoma of the adrenal cortex.

Courtesy of Jonathan Kruskal, MD.
(A) Axial image from abdominal CT scan shows an 11 x 15 cm mixed signal intensity right adrenal mass (arrow) with large amounts of macroscopic fat consistent with adrenal myelolipoma.

(B) Gross pathology cut section showing a 19 x 12 x 9.5 1030 gm adrenal myelolipoma.
Thank You for your attention!