Adrenal gland disorders

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Adrenal glands:

Niemann LK. UpToDate®, Vol. 17, No. 3.
Physiology:

Stewart PM. William’s Textbook of Endocrinology, 10th edition.
Adrenal medulla:

Adrenal cortex is a true endocrine gland.

Adrenal medulla is a modified sympathetic ganglion.

The chromaffin cell is a modified postganglionic sympathetic neuron.

Epinephrine is a neurohormone that enters the blood.

To target tissues
BIOSYNTHETIC PATHWAYS FOR CATECHOLAMINES

CATECHOL
L-tyrosine → L-dopa → Dopamine → L-norepinephrine → L-epinephrine
Patient T.M., 1962 (38 yrs):

- **SNMP (10.6.2000):** so tired, that he barely walks, epigastric pain, RR 100/70, Na$^+$ 127 mmol/l → Apaurin 2 mg, Buscopan 1 amp.

- **SNMP (13.6.2000):** feeling ill for 14 days, lost 7 kg, severe gastric pain, vomited several times, without energy → Rupurut, Ranital do not help;

- **Psychiatrist (13.6.2000):** dextrose 5% infusion + vitamin B1, B6, Apaurin; Rp. for Eglonyl, checkup in 1 week.

- **SNMP (18.6.2000):** epigastric pain, diarrhoea, vomiting, anorexia, pain in arms and legs, RR 85/60, fr. 120/min; lab.: glc 6.0, K$^+$ 7.8, Na$^+$ 118, creat 289, BUN 36.2, CK 11.4, myoglobin 622, Hmg: L 6.1, no left shift, Hb 159, CRP 15 → IPP
IPP → CIIM - 18.6.2000:

- **IPP (18.6.2000):** seriously ill, pale, no peripheral pulses, peripheral cyanosis; Haes 500 ml i.v. Dg. Shock, Acute kidney failure → CIIM.

- **CIIM (18.6.2000):** RR 80/40 → Th.: Haes 500 ml, CaLeopold 10 ml i.v., 40% dextrose+32 E ARH/100 ml/h, 1M NaHCO3 100 ml, Sorbisterid, Torecan, Dopamin, normal saline infusion; microbiological tests, ECG, x-rays, abdominal US, Echocardiogram; ACTH stimulation test scheduled for next day!
ACTH stimulation test:

- ACTH
- Cortisol

nmol/l

500
ACTH

cortisol

nmol/l  500
SERUM CORTISOL AFTER ACTH:

nmol/l

500

controls patients
CIIM - 19.6.2000:

- fever (38.3), WBC and CRP normal, RR around 80/30 mmHg.
- Lab.: Na\(^+\) 119 mmol/l, K\(^+\) 6.9 mmol/l, creatinine 240, BUN 30.7
- ACTH stimulation test performed, but still no result.
- endocrinologist: treat as addisonian (adrenal) crisis

- ACTH test i.v.: cortisol 25.9 → 28.4 nmol/l
100 mg of hydrocortisone in infusion/8 h

Hydrocortisone 100 mg bolus i.v.

4 - 6 l of 5% dextrose in normal saline/24 h
CIIM - 20.6.2000:

• Patient is better, still mildly elevated temperature (37.4), WBC and CRP normal, RR around 120/70 mmHg. Dopamin//ex.

• **Lab:** Na⁺ 130 mmol/l, K⁺ 4.6 mmol/l, creatinine 129, BUN 17.3

• **endocrinologist:** hydrocortisone 50 mg/8h i.v., transfer to ENDO when possible
• **Discharge diagnoses:** Addisonian crisis, Hypovolemic shock.

• **ENDO:** History of asthenia lasting more than one year, often tired. Abdominal pain, diarrhoea, nausea, vomiting, even less energy than usual, no appetite, only fluids for almost three weeks; severe pain in fingers on the last day.

• The patient is hyperpigmented, especially on lower lip and palmar creases; mildly tachypnoic, RR 130/50 mmHg, hypervolemic, few inspiratory rales, better after diuretic and fluid restriction.

• **Lab:** Na⁺ 131 mmol/l, K⁺ 4.4 mmol/l, creatinine 97, BUN 8.7, Hb 92 g/l.

• Th.: Hydrocortisone 25 mg/8h i.v.
### Chronic adrenal failure:

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>100</td>
</tr>
<tr>
<td>Anorexia</td>
<td>100</td>
</tr>
<tr>
<td>GIT symptoms</td>
<td>92</td>
</tr>
<tr>
<td>Nausea</td>
<td>86</td>
</tr>
<tr>
<td>Vomiting</td>
<td>75</td>
</tr>
<tr>
<td>Constipation</td>
<td>33</td>
</tr>
<tr>
<td>Weight loss</td>
<td>100</td>
</tr>
<tr>
<td>Hypotension</td>
<td>88 – 94</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>94</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>10 – 20</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>88</td>
</tr>
<tr>
<td>Hyperkaliemia</td>
<td>64</td>
</tr>
<tr>
<td>Elevated creatinine, BUN</td>
<td>55</td>
</tr>
<tr>
<td>Anemia</td>
<td>40</td>
</tr>
</tbody>
</table>

Burke CW. Clin Endocrinol Metab 1985; 14: 947.
Clinical features:
Chronic insufficiency

Acute insufficiency

“Critically ill”

- infection
- dehydration
- surgery
- trauma
- ACS
- childbirth
• hydrocortisone dose is lowered (p/o)

• additional tests:
  - ACTH 155 (- 10.2)
  - PRA **11.8** (- 4.26)
  - cortisole profile
  - TSH 6.10, pT₄, pT₃, thyroid Ab, thyroid ultrasound normal

• **Adrenal CT scan:** bilateral atrophy
ENDO 25.6.00 → AMB.:

- Discharge diagnoses: Addisonian crisis, Acute gastroenterocolitis, Mb. Addison
- Discharge Th.:
  - Hydrocortisone 15 mg (8h) + 10 mg(13h)+ 5mg(17h) + instructions
  - Astonin H (fludrocortisone) ½ tbl/day
- ENDO outpatient clinic:
  patient feels well, regular checkups
Other causes of adrenal insufficiency:
Patient T.V., 26 yrs

- Feb. 2004: severe headaches → neuro.: “migraine”
- Nov. 2004: palpitation, AH → cardio.: propranolol
- Dec. 2004: IPP → cardiology dept.: myocarditis of unknown etiology, art. hypertension → perindopril 4 mg/d, bisoprolol 5 mg/d, spironolacton 25 mg/2.day
- Jan. - April 2005: cardiology outpatient clinic: regular checkups → perindopril 8 mg/d, bisoprolol 7.5 mg/d, spironolacton 25 mg/2.day
- → attacks of high BP (- 240/150 mm Hg), sweating
"5 P" ⇒ Pheochromocytoma:

- Pressure
- Pain
- Palpitation
- Perspiration
- Pallor

Pheochromocytomas:

- Tumors that produce, metabolize and secrete catecholamines.
- In ≈ 0.2 – 0.6% of hypertensive population.
- ~ 50% of these tumors found on autopsy.
- Almost invariably fatal if missed or not properly treated.
- Correct diagnosis enables efficaceous treatment and usually complete recovery.

http://www.endotext.org/adrenal/
Where can we find these tumors?

- adrenal gland (85%)
- paraganglioma (15%)

### Clinical presentation:

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>hypertension</strong> (sustained/paroxysmal)</td>
<td>&gt;90 (60/30)</td>
</tr>
<tr>
<td>orthostatic hypotension</td>
<td>10 - 50</td>
</tr>
<tr>
<td>headache</td>
<td>90</td>
</tr>
<tr>
<td>sweating</td>
<td>60-70</td>
</tr>
<tr>
<td>arrhythmias</td>
<td>30 - 40</td>
</tr>
<tr>
<td>pallor/flushing</td>
<td>27/10</td>
</tr>
<tr>
<td>panic attacks</td>
<td>30</td>
</tr>
<tr>
<td>weight loss, fatigue</td>
<td>40 - 50</td>
</tr>
<tr>
<td>constipation, DM</td>
<td></td>
</tr>
<tr>
<td>myocarditis, heart failure, fever</td>
<td></td>
</tr>
</tbody>
</table>

Pheochromocytoma spells:

- Usually last from few seconds to one hour
- Variable frequency (e.g. 1x/2-3 months)
- Unpredictable during rest, exercise, with trauma, childbirth, drugs (opiates, dopamine antagonists, tricyclic antidepressants, cocaine)
- ↑↑ BP and/or arrhythmia during dg. procedures (endoscopy, catheterisation, contrast dyes), anesthesia, micturition, certain food ingestion (e.g. tyramine in chocolate), alcohol

# Biochemical tests:

<table>
<thead>
<tr>
<th></th>
<th>24h urine</th>
<th>Normals</th>
</tr>
</thead>
<tbody>
<tr>
<td>epinephrine</td>
<td>189</td>
<td>do 13.9 nmol/mol kr.</td>
</tr>
<tr>
<td>norepinephrine</td>
<td>392</td>
<td>do 66.1 nmol/mol kr.</td>
</tr>
<tr>
<td>metanephrine</td>
<td>1621</td>
<td>do 200 nmol/mol kr.</td>
</tr>
<tr>
<td>normetanephrine</td>
<td>1909</td>
<td>do 400 nmol/mol kr.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>plasma</th>
<th>Normals</th>
</tr>
</thead>
<tbody>
<tr>
<td>metanephrine</td>
<td>513.4</td>
<td>do 90 ng/l</td>
</tr>
<tr>
<td>normetanephrine</td>
<td>624.3</td>
<td>do 200 ng/l</td>
</tr>
</tbody>
</table>
Imaging methods:

Adrenal CT scan
Functional tests:

$^{123}$I-MIBG scintigraphy
Phenoxyibenzamine (Dibenzyryan®)

intravascular volume

pharmacological blockade before operation!!

liter

5

3

7 14 days
Prognosis:

- BP becomes normal after operation in majority of patients
- Disease can recur, especially in familial forms or paragangliomas (15%)
- Long lasting surveillance - biochemical screening 1x yearly
- MLG pheochromocytoma: 5 - year survival < 50%
- Genetic testing: + fam. history, younger patients, bilateral or multifocal tumors, other signs of hereditary syndromes
• aug. 2006: chest pain, nausea – high BP 190/115 mm Hg: hospital admission for treatment
• Routine dg. procedures: NAD ??
• Th.: metoprolol 2x25 mg, moxonididine 0.4 mg, amlodipine 10 mg, ramipril 10 mg, indapamide 1 tbl
→
• sept. 2006: outpatient checkup:
  - BP 150/105 mm Hg
  - $\downarrow$ K$^+$ 2.7 mmol/l
Primary aldosteronism:

Primary aldosteronism:

- majority (63-91%) of patients has normal $K^+$!

- the most prevalent form of secondary hypertension (5-10%)

When should we screen for primary aldosteronism?

- hypertensive patients with spontaneous ↓ K⁺ and/or profound diuretic-induced ↓ K⁺ (< 3 mmol/l)
- younger patients with hypertension or those refractory to treatment with three or more drugs
- hypertensive patients with adrenal incidentaloma
- [patients with severe hypertension (stage 3 – BP > 180/110 mm Hg)]

Aldosterone should be elevated (≥0.44 nmol/l)

Primary aldosteronism?

What kind of primary aldosteronism?

- Aldosterone producing adenoma (APA)
- Bilateral adrenal hyperplasia (IHA)
- Ectopic tumor
- GRA - FHA I
- FHA II
- Primary adrenal hyperplasia
- Carcinoma

Conn JW. Primary aldosteronism. J Lab Clin Med 1955, 45:661-6

Adenoma

Hyperplasia

- Differential diagnosis?
  - adrenal HRCT/ (MR)
  - adrenal venous sampling

Adrenal CT scan:

, 48 yrs
Adrenal venous sampling:

<table>
<thead>
<tr>
<th>Vein</th>
<th>Aldosterone (A) pmol/l</th>
<th>Cortisol (C) nmol/l</th>
<th>A/C Ratio</th>
<th>Aldosterone Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rt adrenal Vein</td>
<td>21,800</td>
<td>30,940</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Lt adrenal Vein</td>
<td>238,100</td>
<td>19,600</td>
<td>12.1</td>
<td>17.3 : 1*</td>
</tr>
<tr>
<td>IVC</td>
<td>2,400</td>
<td>868</td>
<td>2.8</td>
<td></td>
</tr>
</tbody>
</table>

* Left adrenal vein A/C ratio divided by right adrenal vein A/C ratio; IVC, inferior vena cava
Treatment:

- serum potassium normalizes and hypertension improves in all patients postoperatively
- long-term cure: 30 - 72%
- mean cost saving of $20,000 (US)
- **medications** $\rightarrow$ K$^+$, BP, target organs
  - $\rightarrow$ spironolactone
  - $\rightarrow$ eplerenone
  - $\rightarrow$ (amiloride, triamteren)
  - $\rightarrow$ ACE inhibitors & angiotensin receptor antagonists, calcium channel blockers, thiazides (↓ dose)
  - $\rightarrow$ dietary salt restriction

• SB tip 2 na insulinu, AH, HL, manjši CVI • zbolela konec leta 2005:

– povišanje telesne teže

→ ITM 37.7 kg/m²

– okrogel obraz (facies lunata) – porast KT do 190/110 kljub Th. – neurejen krvni sladkor – depresivna, samomorilne misli

• K

+2.44 mmol/l, Na

+147 mmol/l

, 46 yrs:
• DM type 2 on insulin, AH, HL, stroke

• became ill at the end of 2005:
  – increase in body weight: BMI = 37.7kg/m²
  – moon face (facies lunata)
  – BP increases to 190/110 despite Th.
  – unregulated blood sugar
  – depressive, suicidal thoughts

• $K^+ \ 2.44 \text{ mmol/l}, \ Na^+ \ 147 \text{ mmol/l}$
Cushing’s syndrome:

- caused by chronic exposure to excessive levels of glucocorticoid hormones
  - incidence – 5 – 6 cases / million/ year
  - prognosis: 50 % 5yr mortality, if untreated

Stewart PM. William’s Textbook of Endocrinology, 10th edition.
CORTISOL after 1 mg DMT:
46 yrs:

- DM type 2 on insulin, AH, HL, stroke
- became ill at the end of 2005:
  - increase in body weight: BMI = 37.7kg/m²
  - moon face (facies lunata)
  - BP increases to 190/110 despite Th.
  - unregulated blood sugar
  - depressive, suicidal thoughts
- K+ 2.44 mmol/l, Na+ 147 mmol/l
- 2 mg DMT: cortisol 1330 → 1233 nmol/l
- ACTH: 49.1 pmol/l (-10.2 pmol/l)
- Dg.: Cushing's syndrome – ACTH dependent
3a.) 8 mg DMT:
cortisol 1886 nmol/l, ACTH 49.4 pmol/l
Has ACTH ectopic origin?

- **CT head:** pituitary unremarkable
- **CT chest:** a round lesion in the right upper lung lobe
- **Abdominal CT scan:** formation in the left adrenal gland (2 cm), both limbs of right adrenal are thickened
- **octreoscan:** A number of activities in the gut, suspicious accumulation in front of the neck

- **05/24/2006:** transfer to ENDO, UMC Lj
Etiology:

ACTH dependent forms:

- Cushing’s disease (pituitary form) 70%
- ectopic ACTH syndrome 10%
  - small cell lung cancer
  - carcinoid
  - medullary thyroid carcinoma
  - pheochromocytoma
- (ectopic CRH syndrome)

Niemann L. UpToDate®
3b.) MRI of the pituitary:
IPSS – Inferior Petrosal Sinus Sampling:

<table>
<thead>
<tr>
<th></th>
<th>0 min</th>
<th>5 min</th>
<th>10 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left inferior petrosal sinus</td>
<td>18</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>Right inferior petrosal sinus</td>
<td>19</td>
<td>490</td>
<td>300</td>
</tr>
<tr>
<td>Simultaneous peripheral vein</td>
<td>16</td>
<td>17</td>
<td>30</td>
</tr>
</tbody>
</table>
Transphenoidal resection of the tumor:
Complications:

- before surgery:
  - peritonsillar abscess with respiratory distress – transfer to the ENT for drainage and temporary tracheostoma (6/06)

- after surgery:
  - Urinary tract infection (Klebsiella pneum., Enterococcus faec., Candida Alb.), empirically treated with ceftriaxone, which has triggered an acute psychosis with hallucinations (8/06)
  - massive pulmonary embolism with embolus on the bifurcation of the right main pulmonary artery (8/06)
Epilogue (11/06):

- **hormone testing:**
  - short synacthen test i.v.: cortisol 29.5 → 283 nmol/l
  - ACTH 4.14 (- 10.2 pmol/l)
  - cortisol daily curve on hydrocortisone 10 + 5 + 5 mg: 9h: 790, 13h: 121, 17h: 270 nmol/l

- **Other drugs:**
  - L - thyroxine 75 µg, desmopressin
  - repaglinide, atorvastatin, spironolactone
  - risperidone, citalopram, phenitoin
  - calcium carbonate, cholecalcipherol