Adrenal Disorders

Robert G. Dluhy, M.D.

Disclosure:
I do not have any conflicts of interest

Robert G. Dluhy, MD

---

Case 1
28 y.o. male with no significant past medical history presents with 6-8 months of episodic symptoms

He is hypertensive and is admitted to the MICU with BP 210/120 mm Hg, which requires IV nitroprusside

Physical exam is unremarkable. No thyroid mass or goiter. There is no abdominal bruit, palpable abdominal mass and no signs of Cushing's syndrome

---

How would you direct your questioning regarding his episodic symptoms?

Pheochromocytoma
Frequency of Symptoms

- Headache 43-80%
- Sweating 37-71% the 'triad'
- Palpitations 44-71%
- Pallor 42-44%
- Nausea 10-42%
- Tremors 30-38%

Spells are stereotypic and occur randomly

---

Differential Diagnosis

- Anxiety Attacks
- Cocaine or amphetamine use
- Intracranial lesions (sub-arachnoid hemorrhage)
- Measure BP during a spell

---

When to do screening tests?

- Hypertension with symptoms suggesting pheochromocytoma (such as the triad).
- Marked lability of blood pressure
- Hypertension refractory to antihypertensive treatment
- Severe pressor response during anesthesia
- Family history of pheochromocytoma, or familial disorder (eg, MEN)
- All patients with incidentally-discovered adrenal masses.
Catecholamine Metabolism

Norepinephrine → Epinephrine

| Catechol-O-methyl transferase (COMT) |
| Normetanephrine → Metanephrine |

Monamine Oxidase (MAO)

Vanillyl-mandelic Acid (VMA)

Diagnostic Tests

- 24 hour urine 'free' unmetabolized catecholamines and metanephrines
  - improved accuracy when combined
- Plasma catecholamines - not recommended
- Plasma metanephrines (MS, HPLC)
  - No drug interference
  - High sensitivity; lower specificity
  - Pharmacology interference with NE reuptake and MAO inhibitors

The Patient's laboratory evaluation:

- Urine catecholamines:
  - Epinephrine: 20 ug/24 h (0-49)
  - Norepinephrine: 496 ug/24 h (20-100)
  - Normetanephrine: 5429 ug/24 h (50-650)
  - Metanephrine: 116 ug/24 h (30-350)

- Serum:
  - Normetanephrine: 7.84 nmol/L (0-0.89)
  - Metanephrine: 0.76 nmol/L (0-0.49)

- Next Step?
  - Abdominal CT scan (adrenal mass?)

Radiographic Features

Adrenal Pheo
- Usually > 3 cm
- CT density >10 HU (without contrast);
- MR appearance - hyperintense on T2-weighted images

Adrenal Glands Normal: consider MIBG/PET-CT scan

Pre-operative management

- Alpha blockade with phenoxybenzamine
  - Add calcium-channel blocker if resistant hypertension
  - Add beta-blockade if tachycardia or tachyarrhythmia, typically with atenolol
- Salt loading to expand extracellular volume (150-200 mmol/d x 5 days)
- IV Normal saline overnight pre-op

Hereditary Pheochromocytoma

- Inherited as an autosomal dominant trait alone or a component of a phaeochromocytoma-predisposing syndrome.
**Autosomal Dominant Pheochromocytoma-Predisposing Syndromes**

**Clinical Phenotype**

- Multiple Endocrine Neoplasia (MEN) 2A
- Von Hippel-Lindau Disease (retinal cerebellar hemangioblastosis)
- Hereditary Paraganglioma

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTC</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>retinal angioma</td>
<td>Hemangioblastoma CNS</td>
</tr>
<tr>
<td>renal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Extra-adrenal paragangliomas</td>
<td></td>
</tr>
</tbody>
</table>

**Clues for Familial Syndromes in ‘Sporadic’ Pheochromocytoma**

- Young age
- Multiple, extra-adrenal neoplasms
- History of component tumors in first-degree relatives.
- Physical examination
  - thyroid mass (medullary carcinoma of the thyroid), carotid body tumor, retinal angioma

**Pheochromocytoma**

- Rare tumors of the adrenal and extra-adrenal sympathetic tissues
- Most are symptomatic and hypertensive
- Biochemical screening should precede radiographic imaging
- Not rare in patients with incidentally discovered adrenal masses
- 20% ‘sporadic’ tumors have germline mutations

**Case 2**

- Patient was normotensive until the age of 38 when she was diagnosed with hypertension at a routine office visit.
- At age of 42 she has refractory hypertension (four antihypertensives including: lisinopril 20 mg qd, atenolol 50 mg qd, hydrochlorothiazide 12.5 mg qd, and losartan 50 mg qd).
- Her blood pressure measured at home ranged from 130-160/80-90 mmHg.
- She has experienced intermittent Hypokalemia

**Physical Exam**

- Blood pressure of 132/90 mm Hg
- Pulse of 72 beats per minute
- BMI of 26.5 kg/m²
- No carotid, renal, or abdominal bruits, and no abdominal masses or striae
- No lower extremity edema

**What test would you order?**
Laboratory Test | Laboratory Value | Normal Range
---|---|---
AM Cortisol post 1 mg Dexamethasone at 11PM | 0.5 µg/dL | <2.8
Potassium | 3.3 mmol/L | 3.5-5.0
Plasma Aldosterone Concentration (PA) | 25 ng/dL | 4-31 (Upright, normal salt diet)
Plasma Renin Activity (PRA) | <0.1 ng/mL/hr | 0.2-1.6 (Upright, normal salt diet)

**THE PLASMA ALDOSTERONE / RENIN (PA/PRA) RATIO**
- PA (ng/dl) / PRA (ng/ml/hr)
- Increased Ratio indicates need for more definitive (suppression) testing.
- Patient's PA/PRA Ratio = 250. Normal ratio <20

**Primary Aldosteronism**
- ↑ VOLUME
- ↑ Na+ (↓ K⁺)
- ↓ RENIN
- * ALDOSTERONE PRODUCTION
- * Primary Event

**Confirmatory Testing**
- Demonstrate Autonomous Aldosterone secretion
- An oral three day salt-loading suppression test: urine creatinine 1666 mg/24h, urine sodium 327 mmol/24h, and aldosterone excretion rate of 24 ug/24h (normal: <6 ug/24h).

**Differential Diagnosis:**
- Aldosterone Producing adenoma (APA)
- Bilateral adrenal hyperplasia (BAH)
- Adrenal Carcinoma
- Unilateral or primary adrenal hyperplasia
- Glucocorticoid-remediable aldosteronism

**SCREENING TEST**

- An Adrenal Protocol CT Scan with 1.5 mm axial slices was performed.
1.2 X 0.8 cm low attenuating well defined lesion arising from the lateral limb of the left adrenal gland

What next?

Adrenal Vein Sampling

<table>
<thead>
<tr>
<th>Location</th>
<th>Aldo (ng/dL)</th>
<th>Cortisol (ng/dL)</th>
<th>PAC/Cortisol ratio</th>
<th>Aldosterone ratio, Left:Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subrenal IVC</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Right AV</td>
<td>40</td>
<td>16</td>
<td>2.5</td>
<td>Ratio 6</td>
</tr>
<tr>
<td>Left AV</td>
<td>750</td>
<td>50</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

- The patient did meet criteria for lateralization (Ratio > 2)
- A diagnosis of APA was made
- Successful left laparoscopic adrenalectomy was performed

Results of Unilateral Laparoscopic Adrenalectomy for APA

- BP Control
  - 100% improve
  - Long-term cure 30-50%
- Risk factors persistent HTN
  - Family Hx Essential HTN
  - Older age
  - Duration HTN
  - Increase sCr

Case 3

- A 38 y/o male complains of fatigue, loss of appetite, and a 15 pound weight loss.
- Friends have also commented about his increasing skin pigmentation
- His physician notes the hyperpigmentation compared to other family members
- She documents postural hypotension
- Blood testing reveals hyponatremia, hyperkalemia and a 4-fold elevated ACTH level.
- She performs definitive adrenal testing.
Adrenal Insufficiency

Presenting Signs and Symptoms
- Symptoms are non-specific
  - Weakness, fatigue
  - Anorexia/nausea/weight loss
  - Hypoglycemia
- And sometimes (if mineralocorticoid insufficiency)
  - Hypotension
  - Postural dizziness

ACTH (Cosyntropin) stim test
- Measure serum cortisol before and 60 minutes after 250 µg of cosyntropin IV.
- This dose of cosyntropin results in pharmacological plasma ACTH concentrations for 60 mins. Low dose ACTH testing not recommended.
- A serum cortisol value of >18 µg/dL at 60 mins indicates normal adrenal reserve
- A subnormal response diagnoses adrenal insufficiency (AI)

Adrenal Insufficiency

Primary: destruction adrenal cortex (AC)
Secondary: atrophy AC

<table>
<thead>
<tr>
<th>ACTH</th>
<th>PA</th>
<th>PRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

N = Normal
PA = Plasma Aldosterone

Primary AI

Polyglandular Failure Syndromes (autoimmune etiology)

<table>
<thead>
<tr>
<th>PGF-I</th>
<th>PGF-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal insufficiency</td>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>Mucocutaneous candidiasis</td>
<td>Thyroiditis</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Insulin-requiring diabetes</td>
</tr>
<tr>
<td>Alopecia</td>
<td>HLA-88 DW3 association</td>
</tr>
<tr>
<td>Gonadal failure</td>
<td>Pernicious</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>No HLA association</td>
</tr>
</tbody>
</table>

Treatment

- GLUCOCORTICOID REPLACEMENT for primary and secondary adrenal insufficiency
  - Cortisol 8-10mg/m2/day
- MINERALOCORTICOID REPLACEMENT only for primary adrenal insufficiency (AI) (fludrocortisone)

Case #4

46 Year Old Female (Postmenopausal)

8 Month History of:
- facial rounding
- 30 pound weight gain
- ankle swelling
- multiple boney fractures in the spine and ribs
Physical Exam

- T 98.4°F, BP 160/100 mmHg, P 76 BPM
- Obvious Cushingoid features
  - Moon facies
  - Buffalo hump
- 3+ Pitting pretibial edema

Laboratory Studies

<table>
<thead>
<tr>
<th>Blood</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN 12 mg/dl</td>
<td>(9-25)</td>
</tr>
<tr>
<td>Creatinine 1.0 mg/dl</td>
<td>(0.7-1.3)</td>
</tr>
<tr>
<td>Sodium 141 meq/L</td>
<td>(136-142)</td>
</tr>
<tr>
<td>Potassium 2.9 meq/L</td>
<td>(3.5-5.5)</td>
</tr>
<tr>
<td>Chloride 95 meq/L</td>
<td>(94-108)</td>
</tr>
<tr>
<td>Bicarbonate 36 meq/L</td>
<td>(23-32)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline urine free cortisol</td>
<td>2298 mcg/24hr</td>
<td>&lt;50</td>
</tr>
<tr>
<td>8AM ACTH</td>
<td>129 pg/ml</td>
<td>9-52</td>
</tr>
</tbody>
</table>

Is dexamethasone suppression indicated? What is the diagnosis?

Hormone Excess Etiologies

- Cushing’s Syndrome
  - exogenous treatment (iatrogenic)
  - endogenous cortisol overproduction
- Endogenous Cortisol Hypersecretion
  - ACTH dependent
    - Pituitary tumor (Cushing’s Disease)
    - Ectopic production (e.g. Lung Tumor)
  - ACTH independent
    - Adrenocortical tumors
    - Exogenous steroid treatment

Radiographic Studies

- CXR, CT Chest, CT Abdomen, MRI Pituitary: All Normal
What would you do next?

Unstimulated Inferior Petrosal Sinus (IPS) Sampling for ACTH

<table>
<thead>
<tr>
<th>Sample</th>
<th>Right IPS</th>
<th>Left IPS</th>
<th>Peripheral (P)</th>
<th>Maximum IPS:P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>88</td>
<td>86</td>
<td>80</td>
<td>1.1:1</td>
</tr>
<tr>
<td>2</td>
<td>96</td>
<td>85</td>
<td>75</td>
<td>1.3:1</td>
</tr>
</tbody>
</table>

IPS:P <2.0:1 suggests ectopic peripheral ACTH production

Now What?

- An octreotide scan was performed

Octreotide Scan (SPECT)

Follow Up

- 6 months after resection of an ACTH-Secreting pulmonary carcinoid
WHY WAS THIS PATIENT HYPOKALEMIC?

GLUCOCORTICOID SHUTTLE

11 β – HSD 1 (LIVER)

\[
\text{CORTISOL} \quad \rightarrow \quad \text{CORTISONE}
\]

Active

Deficiency

11 β – HSD 2 (KIDNEY)

Deficiency

Inactive

Post-Operative Management

- How would you manage this patient post-operatively?
  - Cortisol yes/no
    - How much?
    - How long?
    - How would you taper?
  - Aldosterone (florinef) yes/no

Take Home Points

1) Approximately 20% of patients with 'sporadic' pheochromocytomas/paragangliomas carry germline mutations. These mutations are inherited in an autosomal dominant fashion; all first-degree relatives of affected probands should be genetically screened.

2) The preferred screening test for primary aldosteronism is measuring the plasma aldosterone/plasma renin activity ratio. Confirmatory testing is accomplished by documenting autonomous aldosterone secretion following oral salt loading.

3) Primary and secondary adrenal hypofunction can be distinguished by assessing ACTH and aldosterone levels. In primary adrenal insufficiency ACTH levels are elevated and aldosterone levels are reduced. In secondary insufficiency ACTH levels are 'inappropriately' normal or low while aldosterone levels are normal due to regulation by the renin-angiotensin system.

4) Cushing's syndrome is diagnosed by determining cortisol over-production. The next step is to determine where the cortisol production is ACTH-independent (adrenal tumors, exogenous glucocorticoid usage) or ACTH-dependent (pituitary or ectopic ACTH-secreting tumors).

Review Question 1

1. A 35 year old male complains of headaches and excessive sweating. His physical examination shows an anxious male with a blood pressure of 186/110 mmHg, pulse 90 bpm. The remainder of the physical examination is normal. Family History reveals that his father died of an abdominal malignancy. Plasma metanephrines are four-fold elevated and he is discovered to have an extra-adrenal abdominal mass. He is suspected of having a hereditary pheochromocytoma syndrome. Which germline gene is the most likely to be mutated?

- A. RET proto-oncogene
- B. VHL gene
- C. NF 1 gene
- D. NF 2 gene
- E. SDHB gene
E. SDHB gene

Review Question 2
2. A 61 year old female has a ten year history of hypertension which has become difficult to control. She is being treated with amlodipine 10mg qd, lisinopril 20mg qd and hydrochlorothiazide 25 mg qd. Her physical examination shows a BP of 160/90 mmHg and a HR 74 bpm. Her lab values show a potassium level of 3.3 meq/L (normal 3.5-5) and normal renal function. An aldo/renin ratio is elevated (70; normal <20). The next best step is to:

- A. Obtain an abdominal CT scan, adrenal protocol
- B. Perform adrenal vein sampling
- C. Discontinue the lisinopril and repeat the aldo/renin ratio
- D. Discontinue the amlodipine and repeat the aldo/renin ratio
- E. Perform a salt suppression study

References