Adrenal Disorders for Non-Endocrinologists

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Objectives

• Adrenal Incidentaloma
  – Subclinical Cushing’s syndrome
  – Pheochromocytoma
  – Hyperaldosteronism
  – DHEA-S producing tumors

• Adrenal Insufficiency vs. Adrenal Fatigue (if time permits)

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ADRENAL INCIDENTALOMA
Definition

► “Mass lesion greater than 1 cm in diameter discovered “accidentally” during a radiographic examination performed for indications other than an evaluation for adrenal disease.”

Prevalence

- Autopsies: 87,065 cases: 6% with adrenal adenomas
- Abdominal CT (61,054 CT scans reviewed): 4%
- In general, ranges 1-9%
- Majority of incidentalomas are clinically nonfunctioning, benign adenomas
Incidence Increases with Age

Endocrine and Metabolism Clinics of North America. 2000; 29(1):159-185
Two Main Questions

• Is the adrenal mass hormonally active?
• Is the mass benign or malignant?
  • Is it metastatic?
Another Question

• Why don’t ants get sick?

• Because they have little ANTY bodies.
Anatomy

- Primary Aldosteronism
- Cushing’s Syndrome
- DHEA-s
- Pheochromocytoma
Frequency of Findings

- Multicenter study of 1096 cases
  - Nonfunctioning adenoma: 85%
  - Subclinical Cushing’s syndrome: 9%
  - Pheochromocytoma: 4%
  - Aldosteronomas: 2%

Frequency of Findings

- SCCS: 11%
- Pheochromocytoma: 7.5%
- Conn’s syndrome: 2%
- Non-functional: 79.5%

Hyperfunctioning Hormonal Evaluation

• Subclinical Cushing’s Syndrome
• Pheochromocytoma
• Primary Aldosteronism
• Sex-hormone secreting adrenocortical tumors
Subclinical Cushing’s Syndrome

- Central obesity
- Facial rounding
- Buffalo hump
- Easy bruising
- Purple striae
- Proximal muscle weakness
- Emotional/cognitive changes
Cushing’s Syndrome

buffalo hump
Cushing’s Syndrome

Easy bruising
Cushing’s Syndrome

purple stretch marks
Subclinical Cushing’s Syndrome

► Increase risk for:
  – Hypertension
  – Dyslipidemia
  – Impaired glucose tolerance
  – Type 2 DM
  – Atherosclerosis
  – Osteoporosis?

Tauchmanova L, et. al. Patients with subclinical Cushing’s syndrome due to adrenal adenoma have increase cardiovascular risk. JCEM 2000; 85:1440.
Subclinical Cushing’s Syndrome

- Biochemical abnormalities
  - Elevated urine free cortisol
  - Low or suppressed ACTH
  - Blunted diurnal variation
  - No cortisol suppression after 1 mg overnight dexamethasone suppression test

Best Screening Test

Dexamethasone Suppression Test

- 1 mg dexamethasone at 11PM
- Measure cortisol at 8-9AM the next morning
  - Normal: cortisol < 5 μg/dL
- Specificity of DST is 91%
  - Severe bipolar depression and severe alcoholism can give false positive results

- If the DST 8AM serum cortisol is abnormal, then baseline ACTH, serum and 24-hour urinary cortisol should be obtained to confirm autonomy
Hyperfunctioning Hormonal Evaluation

• Subclinical Cushing’s Syndrome
• Pheochromocytoma
• Primary Aldosteronism
• Sex-hormone secreting adrenocortical tumors
**Pheochromocytoma**

- Rare but fatal catecholamines producing tumor
- Incidence: 2-8/million people/year
- Account for 5% of adrenal incidentaloma
- Rule of 10s:
  - 10% extra-adrenal, 10% bilateral, 10% familial, 10% malignant
- Aside from catecholamines, it can also secrete dopamine, ACTH, PTH, calcitonin, VIP
Pheochromocytoma

• Classic triads:
  • Sudden severe headache
  • Diaphoresis
  • Palpitations

• 94% specificity; 91% sensitivity in hypertensive population
Pheochromocytoma

• Available Tests:
  – Plasma fractionated free metanephrines
  – 24-hour urinary fractionated metanephrines and catecholamines
  – Plasma catecholamines
  – Urinary total metanephrines
  – Urinary vanillylmandelic acid

► Which test is best?
• Sensitivity was highest for fractionated PLASMA free metanephrines (99 percent)

• Using receiver operating characteristic curves, sensitivity values at different upper reference limits were highest for fractionated plasma free metanephrines.

• “Fractionated plasma free metanephrines were the best test for excluding pheochromocytoma and should be the diagnostic test of first choice.”
Literature Supports

- **PLASMA** free metanephrines - **BEST** screening test
  - When the test is negative - practically rules out pheo
  - Cost $100 per test

- **URINARY** metanephrines - less sensitive

- Urinary VMA is outdated

Presented at the First International meeting on Adrenal Disease, 2002
Brazil J Med Biol Res 33(10) 2000
NIH State-of-the Science Conference Statement

• Final Statement 7/16/2002
  – “Plasma free metanephrines are recommended as the test of choice for excluding or confirming the diagnosis of pheochromocytoma.”

Management of the clinically inapparent adrenal mass (incidentaloma). NIH State-of-the-Science Conference Statement Feb 4-6, 2002
The first initial test of choice for low risk patients is the 24-hour urinary fractionated metanephrines and catecholamines.

Although elevated levels of fractionated plasma metanephrines have high sensitivity for pheo (99%), the test has a low specificity (85%) and thus should be used when suspicion is high.
What to do?

• Plasma fractionated metanephrines
  – Sens: 99%, Spec 85%

• Urinary fractionated metanephrines and catecholamines
  – Sens: 91%, Spec 98%

• Both are fine. Do the test that is better supported by your clinical practice or environment
Hyperfunctioning Hormonal Evaluation

- Subclinical Cushing’s Syndrome
- Pheochromocytoma
- Primary Aldosteronism
- Sex-hormone secreting adrenocortical tumors
Primary Hyperaldosteronism

• Disorder characterized by high aldosterone secretion

• Account for 10-15% of patients with resistant hypertension
  – 1 in 3 (70 millions) adults in the US affected by hypertension
  – Globally 1 billion
When to suspect PA?

- Adrenal incidentaloma
- Resistant HTN: BP > 140/90 on 3 or more HTN meds, one of which is a diuretic at maximum dose
- Age < 30 with stage 1 HTN (140-159/90-99), a negative family history, and no obesity
Pathophysiology

The Renin-angiotensin-aldosterone Cascade

Reduced blood volume (ECV) or pressure decrease NaCl delivery to macula densa
Increased sympathetic tone or reduced [NaCl] in macula densa release renin

ACTH

Aldosterone

K^+

Angiotensin II

ACE

Angiotensin I

Renin

Angiotensinogen

JG -cells β-receptors

Increased blood volume (ECV)

Inhibition

Proximal reabsorption

Inhibition

Increased reabsorption of Na^+ and water
Inhibition

Increased K^+ secretion

Fig. 24-5

KMc
Physiology (distal tubule)
Primary HyperAldosteronism

• Signs/Symptoms:
  – high blood pressure
  – hypokalemia
  – metabolic alkalosis
  – low renin activity
Screening

• Plasma Aldosterone Concentration (PAC)
• Plasma Renin Activity (PRA)
• PAC/PRA ratio

• PAC/PRA >20 AND
• PAC >15 = POSITIVE SCREEN
• 90% Spec and Sens for PA
PAC/PRA

- This ratio is denominator-dependent
- The lower limit of detection varies among different PRA assays and can have a dramatic effect on the PAC/PRA ratio.

Example 1: PAC 6 ng/dL, PRA 0.6 ng/ml/hr
Ratio: 10

Example 2: PAC 6 ng/dL, but PRA 0.1 ng/ml/hr
Ratio: 60
Criteria: PAC/PRA >20; PAC >15

- Need to look at PAC as well and not just the ratio
**QUIZ**

- Who has primary hyperaldosteronism?

<table>
<thead>
<tr>
<th>Aldo (ng/dL)</th>
<th>PRA (ng/mL•h)</th>
<th>ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>3.3</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>30</td>
</tr>
<tr>
<td>15</td>
<td>1.0</td>
<td>15</td>
</tr>
<tr>
<td>15</td>
<td>&lt;0.6</td>
<td>&gt;25</td>
</tr>
</tbody>
</table>
Primary HyperAldo

• If screening test is positive- need to **confirm** with saline suppression test, adrenal venous sampling and imaging
Confirmation of Diagnosis

• An elevated PAC/PRA ratio is not diagnostic by itself as other mineralocorticoid-excess states exists with low renin.

• Primary aldosteronism must be confirmed by demonstrating inappropriate aldosterone secretion.
Inappropriate Aldosterone Secretion

• 4 Methods:
  – Oral NaCl loading and measurement of urine aldosterone
  – IV NaCl loading and measurement of PAC
  – Fludrocortisone Suppression Test
  – Captopril Test
Oral Sodium Loading

- Maintain 218 mEq NaCl/day or
- Administer two 1g NaCl tablets TID
Oral Sodium Loading

- Maintain 218 mEq NaCl/day or administer two 1g NaCl tablets TID (to give approximately 90 mEq of Na)
- On the third day, measure 24 hr urine aldosterone, sodium, creatinine and serum electrolytes.
- Urine Na should be >200 mEq to document adequate sodium loading
- Urine aldosterone excretion >12 μg/24 hr is consistent with primary aldosteronism
IV Sodium Loading

- Give 2 liters of isotonic saline over 4 hours
- The PAC will fall below 6 ng/dL in normal subjects, whereas values above 10 ng/dL are consistent with primary aldosteronism.
<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Prevalence</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone Producing Adenoma (APA)</td>
<td>30%</td>
<td>Surgery</td>
</tr>
<tr>
<td>Bilateral Adrenal Hyperplasia (IHA)</td>
<td>65%</td>
<td>Medications</td>
</tr>
<tr>
<td>Primary (unilateral) Adrenal Hyperplasia (PAH)</td>
<td>1%</td>
<td>Surgery</td>
</tr>
<tr>
<td>Glucocorticoid-Remediable Aldosteronism (GRA or FH I)</td>
<td>1%</td>
<td>Steroids</td>
</tr>
<tr>
<td>Adrenal Carcinoma</td>
<td>&lt;1%</td>
<td>Surgery</td>
</tr>
<tr>
<td>Ectopic</td>
<td>&lt;1%</td>
<td></td>
</tr>
</tbody>
</table>
Mayo Clinic Study

- 203 patients with primary aldosteronism were evaluated with both CT and adrenal vein sampling, CT was accurate in only 53% of patients.
- Based upon CT, 42 (22%) patients would have been incorrectly excluded as candidates for adrenalectomy, and 48 (25%) might have had unnecessary surgery.

Young, WF. Role of adrenal venous sampling in primary aldosteronism. Surgery 2004; 136:1227
Adrenal Venous Sampling

- Gold Standard to distinguish between an adenoma and hyperplasia
- Protocols vary
  - Cannulation of left/right adrenal vein and IVC
  - Measure cortisol and aldosterone in each vein
  - Cortisol value should be 10 times higher in the adrenal veins compared to IVC
  - **Cortisol-correcting aldosterone** ratio should be 4X higher in the adenoma side compared to the other.
  - ACTH is often used to acutely stimulates aldosterone release and increases the difference between the two sides.
Anatomy of Adrenal Vein

Aldo/cortisol
Patient has a **right** adrenal adenoma- **right** adrenalectomy.
Our patient’s AVS

<table>
<thead>
<tr>
<th>Vein</th>
<th>Aldo</th>
<th>Cortisol</th>
<th>A/C Ratio</th>
<th>Absolute Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rt. Adrenal</td>
<td>143</td>
<td>28.2</td>
<td>5.07</td>
<td>??</td>
</tr>
<tr>
<td>Left adrenal</td>
<td>179</td>
<td>249</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>IVC</td>
<td>72</td>
<td>18.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No Success!
Hyperfunctioning Hormonal Evaluation

- Subclinical Cushing’s Syndrome
- Pheochromocytoma
- Primary Aldosteronism
- Sex-hormone secreting adrenocortical tumors
Sex hormone-secreting Adrenocortical Tumors

- Rare
- Typically occur in the presence of clinical manifestations (hirsutism or virilization)
Sex hormone-secreting Adrenocortical Tumors

• Rare

• Typically occur in the presence of clinical manifestations (hirsutism or virilization)

• Routine screening for excess androgens and estrogens is not warranted
Hormonal Workup Summary

• 3 hormonal tests necessary for workup of adrenal incidentaloma:
  • 1 mg overnight dexamethasone suppresion test
  • Plasma metanephrines or 24 hr urinary fractionated metanephrines and catecholamines
  • Plasma aldosterone concentration and plasma aldosterone concentration/plasma renin activity ratio (PAC/PRA).
Treatment

• All patients with documented pheochromocytoma and primary aldosteronism should undergo surgery

• No prospective, randomized trials for Subclinical Cushing’s Syndrome but concensus is to proceed with surgery if the patient is young
Burning Questions

- Is the adrenal mass hormonally active?
- Is the mass benign or malignant?
- Is it metastatic?

Primary Adrenal Carcinoma

- Very rare: 5 cases per 1 million population
- Small size corresponds to better prognosis
- 5 year survival
  - Overall: **16%**
  - Localized disease (stage I and II): **42%**
  - Metastases: **5.3%**
Patient with Known Malignancy

- 10-40% of patients with known malignancy have adrenal metastases at autopsy
- Most common primary:
  - Breast
  - Lung
  - Kidney
  - Melanoma
  - Lymphoma
Assessment of Malignant Potential

• Imaging Phenotype (features)
• Size
Size

• Probability of malignancy increases with size
  • In a study involving 887 patients with adrenal incidentalomas, 90% of patients with adrenal carcinomas has tumor > 4 cm
  
  (National Italian Study Group, 1997)
Size

- Mayo Clinic Study
  - 342 Patients with adrenal incidentaloma retrospectively evaluated
  - Tumor diameter averaged 2.5 cm
  - Most malignant tumors measured > 5 cm

- Incidentally discovered adrenal tumors: an institutional perspective. Herrera MF; Grant CS; van Heerden JA; Sheedy PF; Ilstrup DM. Surgery 1991 Dec;110(6):1014-21
Size

- Consensus Statement
  - Mass > 6 cm should be removed
  - Mass < 4 cm can be monitored
  - Mass between 4-6 cm: Criteria other than size should be used to dictate surgery vs. monitoring

Assessment of Malignant Potential

- Size
- Imaging Phenotype (features)
Image Phenotype- CT Scan

- Hounsfield unit (HU)- semiquantitative method for measuring x-ray attenuation
  - Water= 0 HU
  - Adipose tissue= -20 to -150 HU
  - Kidney= 20 to 50 HU
  - Bone= 1000 HU
- Lipid rich mass are benign
  - HU<10 on unenhanced CT= benign adenoma 100%
Hounsfield Units
Image Phenotype- CT Scan

• **Contrast washout**
  - On contrast-enhanced CT, adenomas exhibit rapid washout compared to non-adenomas (metastases, angiosarcoma, pheo, carcinoma...)
  - Wash out of > 50% at 10 min = no cancer
  - Wash out < 50% at 10 min = high risk for malignant lesion
MRI

- Equally effective as CT
- Adenomas are isointense with the liver on T2 weighted images
- Carcinomas are hyperintense compared to the liver on T2 weighted images
Imaging
PET/CT

• Sensitivity of 98.5% and specificity of 98%
PET/CT
What about **Fine Needle Aspiration**?

- **Very limited role!**
- Cytology from FNA cannot distinguish benign adrenal mass vs. malignant
- FNA can only tell you 1) metastases, 2) infection
- Need to rule out pheochromocytoma before FNA
Take Home Points

• All patients with an incidentaloma should have a 1-mg dexamethasone suppression test, a plasma/urinary fractionated metanephrines and a aldosterone/renin level

• A homogenous mass with low attenuation value (HU<10) on unenhanced CT is a benign adenoma

• Surgery should be considered in all patients with functioning adrenal cortical tumors or with pheochromocytoma
• Data are insufficient to indicate superiority of a surgical or non-surgical approach to manage patients with subclinical Cushing’s syndrome

• Patients with tumor $>6$ cm need to have the tumor removed, those with tumor $<4$ cm are typically monitored

• Tumors between 4 to 6 cm need to consider other criteria other than size
Take Home Points (3)

• Continue radiographic reevaluation at 6 months and then annually for 2 years.
• Hormonal evaluation should be performed at time of diagnosis and annually for up to 4-5 years.
• If tumor grow more than 1 cm or become hormonally active during follow-up, surgical excision should be considered.