The Clinician and Endocrine Hypertension: Pitfalls in Evaluation and Management

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Overview

- Endocrine hypertension
  - When and What?

- The major concerns
  - Primary Hyperaldosteronism
  - Pheochromocytoma

- Other considerations in endocrine hypertension
DEMOGRAPHICS OF ENDOCRINE HTN

### Causes of Hypertension

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>General pop’n</th>
<th>Specialty pop’n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential</td>
<td>92-94</td>
<td>65-85</td>
</tr>
<tr>
<td>Renal (parenchymal, renovascular)</td>
<td>3-5</td>
<td>8-20</td>
</tr>
<tr>
<td>Endocrine</td>
<td>2-4</td>
<td>2-14</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

From Harrison’s 11th ed.
Endocrine Causes of HTN

- “Common” causes
  - Primary Hyperaldosteronism (Mineralocorticoid excess)

- “Rare” causes
  - Pheochromocytoma (Catecholamine excess)
  - Cushing syndrome (Cortisol excess)

- “Rarer” causes
  - Unusual forms of congenital adrenal hyperplasia (CAH)
  - Syndromes that mimic mineralocorticoid excess
    - Renal tubular defects (Liddle syndrome, Bartter syndrome, Gitelman syndrome)
    - Syndrome of apparent mineralocorticoid excess (AME)
    - Licorice ingestion

- Other endocrine considerations
  - Hypothyroidism
  - Acromegaly
  - OCPs

PRIMARY HYPERALDOSTERONISM
Primary Hyperaldosteronism (PA)

- Aldosterone is a steroid hormone secreted from adrenal glomerulosa cells
  - Important for salt/water balance
    - Promotes retention of salt/water in order to maintain blood volume/blood pressure

- Effects mediated by the mineralocorticoid receptor (MR)
  - MR is a member of steroid-hormone receptor superfamily
    - Intracellular receptor
    - Steroids diffuse through cell membrane to get to receptor
    - Activation of receptor promotes transcription of genes promoting Na retention (channels, ATPases)

- Net effect is to promote Na+ retention and enhance K+ secretion
  - Enhanced Na+ status leads to HTN

Regulation of Aldosterone secretion

1. Upright Posture
2. Hemorrhage
3. Diuretics
4. Salt Restriction
5. Edematous States

Circulating Renin Substrate → Renin → Angiotensin I → ACE → Angiotensin II

Hyperkalemia → ACTH → Aldosterone Secretion
Causes of Primary Hyperaldosteronism

- Adrenal tumors
  - Most common cause of primary hyperaldo
  - Most are benign adenomas

- Adrenal hyperplasias
  - Bilateral hyperplasia
    - Idiopathic (?)
    - Ectopic receptor expression (Analogous to ectopic receptor expression is some forms of adrenal Cushing syndrome)
  - Familial HyperAldosteronism
  - Unilateral adrenal hyperplasia

- Approx 30-50% cases of primary hyperaldo are due to bilateral hyperplasia (unlike CS)

Familial Hyperaldosteronism

- Autosomal dominant

- Type I FHA—Glucocorticoid remediable aldosteronism
  - Fusion of CYP11B1 and CYP11B2 genes
  - In 376 subjects (27 kindreds) 18% of patients had CVA, 70% hemorrhagic, with median age just under 32 years (mortality >60%)
    - Aldosterone regulated by ACTH → treat with glucocorticoids!

- Type II FHA—Gordon syndrome
  - Appears much more common genetic cause, although mutations not yet identified

- Type III FHA—KCNJ5 (potassium channel) mutations
  - Severe HTN in pediatric age
How common is Primary Hyperaldosteronism?

- Estimates have generally ranged from 10-20%, although selection bias and verification bias may play a role.

- In the Primary Aldosteronism Prevalence in Hypertension (PAPY) study:
  - 1125 newly diagnosed hypertensives were screened in unbiased fashion.
  - Overall prevalence of PA was 11.2%.
    - Bilateral: 57%
    - Unilateral (APA) 43%

  "Surgically curable"

Rossi et al. 2006 J. Am Coll Cardiol 48:2293-300

Frequency of PA correlates with severity of HTN

- In an analysis of 609 unselected primary care patients with HTN, overall incidence of PA was 6.1%.
- Correlation of incidence with disease severity per JNC VI guidelines showed:

<table>
<thead>
<tr>
<th>Severity</th>
<th>Incidence of hyperaldo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>2%</td>
</tr>
<tr>
<td>Moderate</td>
<td>8%</td>
</tr>
<tr>
<td>Severe</td>
<td>13%</td>
</tr>
</tbody>
</table>

Mosso et al. 2003, Hypertension 42:161-5
Who should be screened for Primary Hyperaldosteronism?

<table>
<thead>
<tr>
<th>Hypertensive Subset</th>
<th>Prevalence; Pretest Probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate-severe hypertension (BP &gt;160/100 mm Hg)</td>
<td>8-13</td>
</tr>
<tr>
<td>Resistant hypertension</td>
<td>17-23</td>
</tr>
<tr>
<td>Defined by BP &gt;140/90 mm Hg despite full doses of 3 complimentary antihypertensive drugs including a diuretic appropriate for level of renal function</td>
<td></td>
</tr>
<tr>
<td>Hypertension with unprovoked hypokalemia associated with renal potassium wasting</td>
<td>50</td>
</tr>
<tr>
<td>Hypertension and an adrenal incidentaloma</td>
<td>1-10</td>
</tr>
<tr>
<td>(1-2 in the absence of severe hypertension or hypokalemia)</td>
<td></td>
</tr>
<tr>
<td>Hypertension and diuretic associated hypokalemia (especially if treatment resistant or in the presence of concomitant use of potassium-sparing diuretics or renin-angiotensin system blocking drugs)</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Hypertensive first degree relatives of persons with PA</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Hypertension and family history of early onset</td>
<td></td>
</tr>
<tr>
<td>Hypertension or stroke (especially cerebral hemorrhage at a young age &lt;40 y)</td>
<td></td>
</tr>
</tbody>
</table>

Funder et al, JCEM 2008 93:3268

How common is “Resistant” HTN?

Incidence and Prognosis of Resistant Hypertension in Hypertensive Patients
Stacie L. Daugherty, MD, MSPH; J. David Powers, MS; David J. Magid, MD, MPH; Heather M. Tavel, BS; Frederick A. Masoudi, MD, MSPH; Karen L. Margolis, MD, MPH; Patrick J. O’Connor, MD, MPH; Joe V. Selby, MD, MPH; P. Michael Ho, MD, PhD

Circulation. 2012;125:1635-1642
Summary of overall findings...

“The rates of diagnosed secondary hypertension causes (aortic coarctation, Cushing syndrome, Pheochromocytoma, and primary aldosteronism) were extremely low (<1%) and did not vary according to resistance status”

Resistant hypertension predicts poor cardiovascular outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Resistant</th>
<th>Nonresistant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>54 (2.1)</td>
<td>290 (1.9)</td>
<td>344 (1.9)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>9 (0.4)</td>
<td>81 (0.5)</td>
<td>90 (0.5)</td>
</tr>
<tr>
<td>Stroke</td>
<td>15 (0.6)</td>
<td>76 (0.5)</td>
<td>91 (0.5)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>10 (0.4)</td>
<td>43 (0.3)</td>
<td>53 (0.3)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>365 (14.5)</td>
<td>1607 (10.4)</td>
<td>1972 (10.9)</td>
</tr>
<tr>
<td>Total events</td>
<td>453 (18.0)</td>
<td>2097 (13.5)</td>
<td>2550 (14.1)</td>
</tr>
<tr>
<td>Total patients</td>
<td>2521</td>
<td>15515</td>
<td>18036</td>
</tr>
</tbody>
</table>

Values are n (%).
Hypokalemia

- As noted, aldosterone promotes hypokalemia by causing Na⁺/K⁺ exchange
- However, in recent studies, incidence of hypokalemia ranges from 18 to 35%
- Therefore, the majority of PA patients will not exhibit hypokalemia
- Note that patients with PA appear to be very sensitive to diuretic-induced hypokalemia

Diagnosis of Primary Hyperaldosteronism

- Screening: Aldo:Renin Ratio (ARR)
  - Primary hyperaldo will have ARR>25, in setting of elevated Aldo
    - Indicates high aldo, low renin state (i.e., renin independent)
    - Aldo must be at least mid-normal
    - Must consider laboratory where test run
      - Aldosterone in ng/dl
      - Renin in ng/ml/hr
Correlation between PRA and Aldo

As PRA drops, ARR increases dramatically

Medication effects on ARR

- In the Endocrine Society guidelines, it is recommended to stop all but the following:
  - Verapamil SR
  - Hydralazine
  - Alpha blockers (prazosin, doxazosin, terazosin)

- If needed, one of these can be substituted for current medical regimen
However…

- A recent study showed that
  - It may not be safe to stop all BP meds in patients
    - 40% of patients were not able to switch meds
    - 6/50 (12%) patients experienced SAE requiring hospitalization
  - It may not be necessary
    - 24/25 patients with PA exhibited elevated ARR on “regular” anti-hypertensives, and remaining patient showed similar findings once K⁺ was corrected
    - Adjustment of medications showed reduction in false positive cases in patients found to have essential hypertension

- In my practice, I typically do not stop medications during evaluation

Fischer et al., Rev Endo Metab Disord 2011

Effect of drug therapy on Aldo/Renin ratio

Schwartz and Turner,
Confirmatory testing?

- Endocrine society guidelines require further testing
  - Depending on cut-offs, specificity of ARR is 83% with 75% sensitivity
  - Patients with extremely high ARR (>40) may not need confirmatory testing
    - Sensitivity 88%, specificity 100%

- Confirmatory tests*
  - Saline suppression test (saline infusion)
  - Oral sodium loading test
  - Fludrocortisone suppression
  - Captopril challenge
  - All are of value, and depend on the comfort of the treating physician

*Instructions for performing/interpreting each test found in the Endocrine Society Clinical guidelines, available at www.endo-society.org
Is further testing necessary?

- Goal of further testing is to determine if PA is caused by an adenoma (unilateral) or a bilateral process
  - 40-60% of PA is caused by a unilateral adenoma

- Further testing is valuable in the setting of patients that are amenable (and suitable) for surgery
  - Medical therapy will work, but may not be as good for the patient in the long-term (cardiovascular outcomes)
  - There is data to support the concept that patients have improved Quality of Life (QOL) after resection of adenoma
    - Sukor et al, JCEM. 2010 95:1360-4

Differential diagnosis of PA: biochemical testing

- Testing to identify a tumor
  - 18-OH-corticosterone:
    - Aldosterone precursor
    - Levels higher in adenomas than hyperplasia
  - 2-hr Posture test
    - Aldo levels normally rise in response to standing
    - If levels fall → adenoma
      - However, ~2/3 of tumors will show a “normal” response in this test. (specific, but not sensitive)
Differential diagnosis of PA: Imaging

- In general, CT scan provides better spatial resolution than other modalities
- However, aldosteronomas may be quite small and difficult to identify
  - Adrenal incidentalomas are also common
  - Sensitivity may be better in younger patients, who have lower baseline incidence of incidentalomas
- In multiple studies, CT correctly identified a surgically-proven adenoma in ~50% of cases
- Functional imaging (e.g., metomidate PET) may be available
  - Although this can identify adrenocortical issue with high specificity/sensitivity, functional differentiation between normal and abnormal adrenal is currently is not feasible.

Adrenal hyperplasia?

Remember that nodules can arise in the setting of hyperplasia
Is there value to additional imaging?

- Radiology report reads: “Adrenal nodules detected by CT. Recommend MRI.”

- Is this a reasonable recommendation?
  - Chemical shift MRI can identify lipid rich adrenal nodules, but this information available from non-contrast CT
  - MRI may be valuable to detect pheo (T2 enhancement) but otherwise adds little to a good CT scan.
  → In general, NO!

The definitive test: Adrenal Vein Sampling

- “Gold standard”
- Definitive diagnosis of unilateral vs bilateral disease

- Requires experienced angio/radiologist!!
  - Catheters introduced to both adrenal veins
  - Sample blood from right, left, peripheral before and after ACTH stimulation
Adrenal Vein Sampling: An Example

Pt: JW, 55 yr old man with HTN, low K, small R-sided adenoma on CT

<table>
<thead>
<tr>
<th></th>
<th>Pre-ACTH</th>
<th>Post-ACTH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>A (Aldo)</td>
<td>1126.8</td>
<td>19.2</td>
</tr>
<tr>
<td>F (cort)</td>
<td>23.6</td>
<td>24.1</td>
</tr>
<tr>
<td>A/F</td>
<td>47.75</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Peripheral stim of cortisol: 3.4 → 20.4 (normal)
Cortisol stimulates normally in adrenal veins
Pre-ACTH: marked lateralization to right side
Post-ACTH: Test mix-up makes data hard to interpret R vs L
A/F ratio <1 in left side all the time, suggesting suppression of left.

THEREFORE, this data localizes Aldo to a right-sided adenoma

If a patient is found to have an adenoma and undergoes surgery, what are the chances of “cure” of the HTN?
- Cohort of 54 patients
- ~40% cured, ~40% markedly improved
- Can take up to 12 months for full effects
- Patients with HTN <6 years and requiring <3 meds more likely to be cured

Role for unilateral adrenalectomy in patients with bilateral disease?

- 40 patients studied at a single institution, who were followed for at least 12 months (median, 56.4 mo)

- Results
  - Hypertension cured in 15%
  - Hypertension improved in 20%
  - Post-op HTN control was 65%, compared with 25% pre-op
  - Improved cardiac parameters such as LV Mass Index

- CONCLUSION: "Although this retrospective analysis of patients from a single center does not permit prediction of response rates among patients diagnosed elsewhere, it suggests that unilateral adrenalectomy can be beneficial in some patients with apparent bilateral PA and should not be dismissed as a treatment option"


Treatment of hyperaldo

- If tumor→localize a good surgeon
  - Most tumors can be removed laparoscopically, or with use of robotic surgery
  - Adrenal cancers can secrete aldosterone, although these are very rare (~2% of cancers)

- If bilateral disease→medical mgmt
  - Mineralocorticoid receptor (MR) antagonists are best therapy
    - Spironolactone and Eplerenone
    - Spironolactone may have significant side FX (esp in males), due to inhibition of androgen receptor (gynecomastia)
    - Eplerenone is available, but generally not recommended as first-line therapy (not FDA-approved indication)
  - If not tolerated, use other anti-hypertensives and manage the potassium as needed
  - Consider genetic testing for Type 1 or Type III familial hyperaldo in the right clinical setting
Eplerenone vs. Spironolactone?

Eplerenone Is Not Superior to Older and Less Expensive Aldosterone Antagonists

Saurav Chatterjee, MD," Chaim Moeller, MD," Nidhi Shah, MD," Oluwaseyi Bolorunduro, MD, MFH,∗
Edgar Lichtenstein, MD,∗ Horkart Maclovits, MD,∗ Dabakrat Mukherjee, MD, MD∗
∗Maimonides Medical Center, Brooklyn, NY; †Texas Tech University Health Sciences Center, El Paso
The American Journal of Medicine, Vol 125, No 8, August 2012

- Meta-analysis of 16 studies
- Although none compared the drugs to each other, data on the effectiveness of each was analyzed, and then compared at the end
- These studies focused on cardiovascular outcomes (i.e., not PA per se)

All cause mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPISHIV-HP</td>
<td>171</td>
<td>1096</td>
<td>0.61 (0.57 - 0.65)</td>
<td>0.61 (0.57 - 0.65)</td>
</tr>
<tr>
<td>EPISHIV-HP</td>
<td>479</td>
<td>3116</td>
<td>0.61 (0.57 - 0.65)</td>
<td>0.61 (0.57 - 0.65)</td>
</tr>
<tr>
<td>Total (90% CI)</td>
<td>4883</td>
<td>4468</td>
<td>0.61 (0.57 - 0.65)</td>
<td>0.61 (0.57 - 0.65)</td>
</tr>
<tr>
<td>Total events</td>
<td>649</td>
<td>187</td>
<td>0.61 (0.57 - 0.65)</td>
<td>0.61 (0.57 - 0.65)</td>
</tr>
<tr>
<td>Heterogeneity: I^2 = 18%</td>
<td>95% CI = 0.22 - 0.39</td>
<td>*Favour experimental</td>
<td>*Favour control</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.33 (P = 0.0097)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<th>Total Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All aldosterone antagonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>315</td>
<td></td>
<td>0.74 (0.61 - 0.88)</td>
<td>0.74 (0.61 - 0.88)</td>
</tr>
<tr>
<td>Spironolactone/Canrenone</td>
<td>315</td>
<td></td>
<td>0.74 (0.61 - 0.88)</td>
<td>0.74 (0.61 - 0.88)</td>
</tr>
<tr>
<td>Total (90% CI)</td>
<td>628</td>
<td></td>
<td>0.74 (0.61 - 0.88)</td>
<td>0.74 (0.61 - 0.88)</td>
</tr>
<tr>
<td>Total events</td>
<td>1628</td>
<td></td>
<td>0.74 (0.61 - 0.88)</td>
<td>0.74 (0.61 - 0.88)</td>
</tr>
<tr>
<td>Heterogeneity: CHI^2 = 1.62 (P = 0.19)</td>
<td>*Favour experimental</td>
<td>*Favour control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.15 (P = 0.0319)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hyperkalemia

![Diagram of Hyperkalemia data with Eplerenone and Spironolactone/Canrenone highlighted.]

Gynecomastia

![Diagram of Gynecomastia data with Eplerenone and Spironolactone/Canrenone highlighted.]

Kirschner
Bottom line from this study

CLINICAL SIGNIFICANCE

- Eplerenone is not as efficacious as older aldosterone antagonists in preventing clinical outcomes.
- Eplerenone poorly justifies its increased expense with available outcomes data.
- Rate of all-cause mortality reduction was less with eplerenone compared with older aldosterone antagonists.
- Rates of hyperkalemia were worse with eplerenone.
- Only gynecomastia appeared to be less with eplerenone usage over older aldosterone antagonists.

Our systematic review of the literature indicates that eplerenone has yet to prove the justification of its expense in terms of reducing clinical endpoints. Only a direct head-to-head comparison between the 2 agents can determine true differences in efficacy.

Eplerenone
50 mg: $2.06 per pill
Spironolactone
50 mg: 0.51 per pill
100 mg: 0.49 per pill

Pharmacychecker.com
3/22/2014

New medications on the horizon

- LCI699 is an inhibitor of Aldo Synthase (CYP11B1)

Amar et al
Hypertension
2010; 56: 831-838
LCI699 - 2

- It is effective at reducing Aldo level with modest effects on BP
- Effectiveness may be limited by steroid blockade and production of precursors with MR activity
- Also appears to affect cortisol synthesis (CYP11B2)
  - Clinical trial using this agent as anti-cortisol drug in progress
- …stay tuned

Clinical take home points: Primary Aldosteronism

- The incidence of PA in a “typical” hypertensive cohort is approximately 10-12%
- Specific populations benefit from screening for PA, although the majority of patients are well controlled medically
- Testing for PA is well standardized. Patients in whom surgery is being considered should go AVS to confirm localization of a tumor
- Spironolactone and eplerenone are both effective MR antagonists. There is insufficient data to indicate that eplerenone is superior
PHEOCHROMOCYTOMA

Pheochromocytoma

- Rare tumor of adrenal medulla
  - Synthesizes and releases catecholamines
    - Norepinephrine
    - Epinephrine
    - Dopamine
  - Releases catecholamines in responses to stress, exercise, insulin, hypotension
    - “Fight or flight” reflex
Incidence of pheos in the hypertensive population

<table>
<thead>
<tr>
<th>Patient Subset</th>
<th>Prevalence; Protect Probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unselected hypertension population</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypertension and suggestive symptoms</td>
<td>0.5</td>
</tr>
<tr>
<td>Adrenal incidentaloma</td>
<td>4</td>
</tr>
<tr>
<td>Hereditary forms of pheochromocytoma</td>
<td></td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type II</td>
<td>30-50</td>
</tr>
<tr>
<td>Von Hippel-Lindau disease</td>
<td>12-20</td>
</tr>
<tr>
<td>Neurofibromatosis type I</td>
<td>1-5</td>
</tr>
<tr>
<td>Familial parangangioma syndrome</td>
<td>20</td>
</tr>
</tbody>
</table>

Pacak et al, Ann Int Med 134:315-32

When to suspect a pheo?

- 3 “classic” symptoms
  - Palpitations
  - Perspiration
  - Pain (headaches)
- Often associated with hypertension

- However, symptoms of a pheo tend to be rather non-specific
  - Postural hypotension
  - Tremor - anxiety
  - Abdominal or chest pain (uncommon)
  - Glucose intolerance
  - Heat intolerance

- Symptoms may also vary depending on primary hormone released
  - Norepinephrine: sustained HTN
  - Epinephrine: episodic HTN, flushing
  - Dopamine: Normotension
Static testing: Pheochromocytomas

- Evaluation for pheochromocytoma takes 2 forms:
  - Plasma metanephrines
    - Highly sensitive, less specific (many false positives)
  - Urinary metanephrines + catechols
    - Highly sensitive, better specificity, more inconvenience

Tests for pheo – NIH data

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma free metanephrines</td>
<td>99% (211/214)</td>
<td>89% (575/644)</td>
</tr>
<tr>
<td>Plasma catecholamines</td>
<td>84% (178/212)</td>
<td>81% (523/643)</td>
</tr>
<tr>
<td>Urine fractionated metanephrines</td>
<td>97% (102/105)</td>
<td>69% (310/452)</td>
</tr>
<tr>
<td>Urine catecholamines</td>
<td>86% (151/175)</td>
<td>88% (471/535)</td>
</tr>
<tr>
<td>Urine total metanephrines</td>
<td>77% (88/114)</td>
<td>93% (170/183)</td>
</tr>
<tr>
<td>Urine vanillylmandelic acid</td>
<td>64% (96/151)</td>
<td>95% (442/465)</td>
</tr>
</tbody>
</table>

**Note:** The reference limits used to calculate sensitivity and specificity are presented in Table 1. The sensitivities of tests of plasma free and urinary fractionated metanephrines or plasma and urinary catecholamines were determined as the percentage of patients with pheochromocytoma with positive test results for either normetanephrine or metanephrine (i.e., for tests of plasma or urinary metanephrines) or with positive test results for either norepinephrine or epinephrine (i.e., for tests of plasma or urinary catecholamines).

Tests for pheo – Mayo data

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Likelihood ratio of a positive test (95% CI)</th>
<th>Likelihood ratio of a negative test (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractionated plasma metanephrines</td>
<td>30/31</td>
<td>221/261</td>
<td>6.3 (4.7-8.5)</td>
<td>0.04 (0.006–0.26)</td>
</tr>
<tr>
<td>24-h urinary total metanephrines or catecholamines</td>
<td>28/31</td>
<td>257/261</td>
<td>58.9 (22.1-156.9)</td>
<td>0.10 (0.03-0.29)</td>
</tr>
</tbody>
</table>

Sawka et al, JCEM 2003 88:553-558

Testing for pheos

- The single best test likely depends on the level of suspicion
  - Performing test correctly enhances accuracy
    - Interfering substances or medications?
    - Blood measurements made at rest, without stress
    - Accurate 24 hr urine collection (if possible)
  - If suspicion is high, plasma free metanephrines are more sensitive (fewer false negatives)
  - If suspicion is low, urinary total metanephrines + catecholamines is more specific (fewer false positives)
Medications that affect catechol measurements

- Be aware of possible drug effects on measurements
  - Physiologic elevations (e.g. beta-blockers)
  - Assay interference
    - Acetaminophen
    - Labetalol
    - L-DOPA/Carbidopa (Sinemet)

Disorders that may mimic the biochemistry of pheochromocytoma

1) Acute myocardial ischemia or infarction
2) Acute cerebrovascular event
3) Severe congestive heart failure
4) Acute clonidine withdrawal
5) Acute alcohol withdrawal
6) Monotherapy with pure arterial vasodilators (as hydralazine or minoxidil)
7) Cocaine abuse

Karagiannis et al., Pheochromocytoma: an update on genetics and management
Endocr Relat Cancer, 2007 14: 935-956
Patients with significant tumors usually are biochemically “obvious”

<table>
<thead>
<tr>
<th>Biochemical test (assay method)</th>
<th>Upper reference limits (true negatives &gt;&gt; false negatives)</th>
<th>Tumor possible (false positives &gt;&gt; true positives)</th>
<th>Tumor likely (true positives &gt;&gt; false positives)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Catecholamines (HPLC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine (pg/mL)</td>
<td>498</td>
<td>&gt;498 and &lt;2000</td>
<td>&gt;2000</td>
</tr>
<tr>
<td>Epinephrine (pg/mL)</td>
<td>83</td>
<td>&gt;83 and &lt;400</td>
<td>&gt;400</td>
</tr>
<tr>
<td>6. Free metanephrines (HPLC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normetanephrine (pg/mL)</td>
<td>112</td>
<td>&gt;112 and &lt;400</td>
<td>&gt;400</td>
</tr>
<tr>
<td>Metanephrine (pg/mL)</td>
<td>61</td>
<td>&gt;61 and &lt;220</td>
<td>&gt;220</td>
</tr>
</tbody>
</table>

Confirmatory tests for pheo

- **Clonidine suppression**
  - 0.3 mg of clonidine given po
  - Measure plasma MN at 0, 3 hrs
    - Normal patients will suppress >50% or to normal range

- **Glucagon stimulation**
  - 1 mg glucagon given IV
  - Measure catechols at 0, 2-3 min
    - Stimulation indicates a pheo
    - Potentially dangerous?

- **Phentolamine**
  - Give 1-5 mg phentolamine IV
  - >35/25 drop in BP within 2-10 min is diagnostic
Biochemical diagnosis should precede any imaging study.

In general, dedicated adrenal CT provides best anatomic resolution.
- Average diameter of symptomatic pheo is 4.5 cm.

MRI can be helpful with Differential diagnosis.

MIBG specific but not very sensitive.

MIBG and/or PET most helpful when tumor biochemistry is clear but tumor not localized or suspicion of metastatic pheo.

MIBG scan - ideal

(False color)
MIBG scan - Actual

IMPRESSION: Status post left adrenalectomy. Focal increased activity within the right adrenal gland could represent normal physiologic activity versus pheochromocytoma with appropriate clinical setting.

- Metanephrine 0.23  
  - NI: <0.45
- Normetanephrine 23.0  
  - NI: <0.9
MIBG in metastatic pheo

Pheo: MRI

Note the poorer spatial resolution!
FDG PET showing metastatic Pheo

Management of Pheochromocytoma

- Medical therapy for acute symptoms: Alpha blockade
  - Phentolamine (Regitine)
    - IV agent producing rapid response
  - Oral alpha blockers
    - Slower but more sustainable response
    - Phenoxybenzamine (Dibenzyline), doxazosin, prazosin
  - May also beta-blockade, but only after adequate alpha blockade
    - Unopposed alpha -> severe vasoconstriction

- Surgery as soon as possible (after alpha blockade)
  - Laparoscopic surgery effective and safe
  - Patients at risk for hemodynamic perturbations, so experienced centers are best
Genetics of Pheochromocytomas

- Pheochromocytomas are often (20-25%) associated with germline mutations. These patients are at risk for recurrent pheos and/or other tumors
  - MEN2 (MTC, hyperpara, 2B: mucosal ganglioneuromas)
  - Von Hippel-Lindau (renal CA, hemangioblastoma)
  - Neurofibromatosis type 1 (neurofibromas, CNS tumors, CALS)
  - SDH mutations
    - May be extra-adrenal (SDHC,D)
    - May be malignant (SDHB)

- A good family history is essential in any patient and strong consideration should be given to genetic testing
  - Consideration for family testing if mutation found

Clinical Take home points: Pheochromocytoma

- Biochemical diagnosis of pheo should precede any imaging studies
  - Be aware of effects of medications on test results
- Clinically significant pheos are almost always radiologically evident
- Functional imaging with MIBG has high specificity but low sensitivity. FDG PET probably more sensitive for detecting occult disease
RARE AND RARER CAUSES OF ENDOCRINE HTN

Cortisol and defects in cortisol metabolism

- Patients with Cushing syndrome are at risk for the development of HTN
- Cortisol is a good ligand for the MR, although normally it is metabolized in the kidney to cortisone by 11beta-Hydroxysteroid dehydrogenase (HSD11B2) in the kidney
  - In Cushing syndrome, cortisol production exceeds capacity to metabolize
  - Genetic defects in HSD11B2 cause the syndrome of apparent mineralocorticoid excess (AME)
  - Inhibition of the enzyme by glycerrhizic acid (black licorice) produces the same picture of low aldosterone with HTN/low K+
- Hypercortisolism sufficient to produce HTN is typically clinically obvious
- Combination of new and simultaneous onset of HTN and DM should raise suspicion
Unusual forms of CAH associated with HTN

- An enzymatic defect in 11β-hydroxylase is the second most common variant of CAH and accounts for approximately 5-8% of cases
  - HTN arises due to accumulation of non-aldosterone precursors which retain MR activity (e.g., corticosterone)
  - Hyperandrogenism similar (although possibly not as severe) as 21-OHase deficiency

- CAH and HTN can also be seen in 17α-hydroxylase deficiency.
  - Very rare condition presenting with ambiguous genitalia

Renal tubule defects

- Liddle syndrome is termed “pseudoaldosteronism” because patients also exhibit HTN/low K⁺ in the setting of low aldosterone
  - The defect lies in renal tubule salt handling, the same process normally regulated by Aldosterone
  - Treat Liddle syndrome with low Na diet and K-sparking diuretic (e.g., Amiloride)
  - Autosomal dominant

- Bartter and Gitelman syndromes are also renal salt-handling defects associated with chronic hypokalemia, although are typically not associated with HTN
  - Autosomal recessive
Final Endocrine Considerations

- Thyroid disease
  - Both hyper- and hypo-thyroidism can cause hypertension
    - Hyperthyroidism: via increased inotropy/chronotropy
      - Widened pulse pressure
    - Hypothyroidism: via increased SVR
      - Decreased pulse pressure
- Acromegaly
  - Increased fluid retention, tissue deposition
  - Also characterized by increased SVR

OCPs in HTN

- In a cohort of over 68,000 women followed for 4 years, OCP usage was associated with 1.8-fold increased risk for HTN, which reduced to 1.2-fold with stoppage of medication
- Effect mediated by estrogen-containing OCPs (i.e. not observed in progestin-only formulations)
  - Systolic BP increased by up to 8 mm Hg in some studies
  - May be mediated by E2-mediated increases in angiotensinogen

Chasan-Taber et al, Circulation. 1996 94:483-9
Boldo and White, Endo Metab Clin N Am 2011 419-32
There is good evidence that the progestin drospirenone functions as a mild MR antagonist and counteracts E2 effects
- Found in Yaz, Yasmine, and Ocella

Use of this information in practice?
- For hypertensive women on OCPs, consider
  - Stopping OCPs
  - Switch to formulation with Drospirenone
  - If neither is an option, these patients may respond well to ARBs/ACE-I's or MR antagonists
In summary…

- Primary hyperaldosteronism
  - By far the most common cause of endocrine hypertension
  - Hypokalemia is seen in <50% of cases
  - Because tumors can be small, anatomic imaging has relatively low sensitivity. Patients deserve adrenal vein sampling for localization before surgery

- Pheochromocytomas
  - Patients with actual tumors tend to have very obvious biochemical abnormalities (>3-5 x normal)
  - No imaging until biochemistry is confirmed, although patients tend to have obvious anatomic lesions

- Other causes:
  - If the data does not make sense, keep an open mind for unusual causes of HTN