Endocrine Hypertension: Sorting through Complex Cases

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## 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,</td>
<td>3-5</td>
<td>8-20</td>
</tr>
<tr>
<td>renovascular)</td>
<td></td>
<td></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.*
Mr D is a 56 year old man who presents to his new PCP with a history of hypertension >10 years
- BP Meds: Hyzaar, Nifedipine

Clinically without complaints

PMHx
- BPH, Renal cyst, hyperlipidemia, kidney stone
- Abd GSW requiring laparotomy, but no residual, App-x, GB-x

FamHx:
- Mom: HTN, DM. Father: Kidney disease
ED - 2

- **Meds:**
  - Oxybutinin, Hyzaar, Nifedipine

- **Exam:**
  - BP 160/100 (180/120), HR 72
  - Exam otherwise WNL

- **Labs:**
  - K 3.5, BUN 11, Creat 0.85
Does this gentleman merit evaluation for endocrine causes of HTN?

1. Not necessary
2. Yes, for hyperaldo
3. Yes, for pheo
4. Yes, for something else

Bar chart:
- 1: Not necessary, 20%
- 2: Yes, for hyperaldo, 65%
- 3: Yes, for pheo, 8%
- 4: Yes, for something else, 7%
When should patients be screened for Primary Hyperaldosteronism?

- Stage 2 hypertension
  - SBP 160-179, DBP 100-109
  - Incidence: ~8%
- Drug resistant hypertension
  - Requiring 3 or more drugs
  - Incidence: ~20%
- Hypertensive patients with hypokalemia
  - Spontaneous hypokalemia
  - Diuretic-induced hypokalemia (?)
  - Incidence: unknown
- Hypertension in patients with adrenal incidentaloma
  - Incidence: ~2%
- Family history of early-onset HTN and/or CVA (<40 yo)
  - Incidence: unknown, although these patients are rare

Endocrine Society Guidelines: 2008
At follow-up (2 weeks later), K=3.1
PCP elects to perform endocrine W/U

Labs:
- Aldo: 19.1 ng/dl (nl 5-19.4)
- Renin: <0.1 ng/ml/hr
- Urine metanephrines WNL
What next?

1. Order additional static testing
2. Order additional dynamic testing
3. Order imaging
4. Start therapy
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 (97)</td>
<td>221/261 (85)</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 (either test positive)</td>
<td>28/31 (90)</td>
<td>257/261 (98)</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
Evaluation for pheochromocytoma takes 2 forms:
- Plasma metanephrines
- Urinary metanephrines + catechols

However, elevated Aldo/renin ratio probably means this is not necessary
Caveat about Aldo/Renin ratio

As PRA drops, ARR increases dramatically

Dynamic testing

- Confirmatory tests for hyperaldosteronism:
  - Oral salt loading test
  - IV saline suppression test
What was actually done:
What’s the diagnosis?

1. Unilateral hyperalado (tumor)
2. Bilateral hyperalado (hyperplasia)
3. Not sure
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.
- 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 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!
What now?

- Confirmatory testing still would be valuable, but likely to be (+)

- Cause of hyperaldosteronism not yet established
  - unilateral (tumor) vs. bilateral (hyperplasia)

- Radiology cannot usually lateralize an aldosteronoma
  - Adrenal incidentalomas may confound
  - Aldosteronomas may be quite small
Differential diagnosis of primary hyperaldosteronism

- Tumors: 50-60% of PHA

- 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)
  - Adrenal vein sampling
    - Needs experienced interventional radiologist
    - Gold standard test
Does it matter?

- Establishing the presence of uni- vs. bi-lateral disease only important if it would affect therapy (e.g., surgery)
  - Bill Young: “4th and Long: Punt or Go For It?”
  - There is data to support that patients have improved QOL after resection of adenoma

- However, this patient was clear that he would not want surgery
  - Empiric therapy started
  - Patient has done better, but we will await long-term outcome as medications titrated
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”

Take home points

- Worthwhile to fully establish diagnosis before treatment or further workup

- In this case, imaging ruled out worry for a cancer, but presence of bilateral nodules makes it of limited value
  - Abd CT should be repeated in 1 year to document stability. If so, further imaging likely not needed

- Workup to distinguish adenoma vs. bilateral hyperplasia only valuable in setting where surgery to be pursued.
Case History: SW

- 56 year old lady presents in 2009 from outside endocrinologist to an OSU surgeon for removal of a 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
Case History: SW

- Patient placed on prazosin pre-op, but stops taking it (instructions). Surgery is cancelled when she presents with BP 180/100 on day of procedure.
- Returns two weeks later on meds with better control of BP. Is admitted 2 days pre-op for optimization of alpha-blockade and fluid status.
- Has uneventful laparoscopic removal of tumor. Pathology confirms pheochromocytoma of 23.8 grams, measuring 7.5 x 2.4 x 2.3 cm. Margins clear.
- No family history to suggest inherited syndrome
  - ~15% of pheos thought to be part of a syndrome
  - w/u of all patients includes a family history.
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
Patient presents to an outside ER (Aug 2011) with complaints of nausea, vomiting, diarrhea, palpitations/tachycardia and headache, which were similar to her initial presentation.

Meds: Toprol XL 50 mg BID

At the outlying hospital, HR was reported to be rates of up to 200, although on review, these were felt to be artifact. She was started on a labetolol drip and transferred to OSU for further evaluation.

On arrival to our ER, BP 125/75 range (on drip). She was having runs of SVT in the 170s felt to be atrial or reentrant tachycardia.

Diagnosis: ?Recurrent pheochromocytoma
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 (Epi, NorEpi, Dopamine)
What next?
Order lab testing plus...

1. CT scan
2. MRI scan
3. MIBG scan
4. PET scan
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 Ddx.

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.
Pheo: CT
Note the poorer spatial resolution!
MIBG scan - ideal

Ant

Post

Posterior

(False color)
FDG PET showing metastatic Pheo
Back to our patient...

She got set of CT images in the ER...
<table>
<thead>
<tr>
<th>Test</th>
<th>Unit</th>
<th>8/26/2011</th>
<th>8/25/2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noradrenaline, Plasma</td>
<td>pg/ml</td>
<td>2186 (H) . . .</td>
<td>(NL &lt; 1700)</td>
</tr>
<tr>
<td>Adrenaline, Plasma</td>
<td></td>
<td>177 (H) . . .</td>
<td>(NL &lt; 110)</td>
</tr>
<tr>
<td>Dopamine, Plasma</td>
<td></td>
<td>116 (H) . . .</td>
<td>(NL &lt; 30)</td>
</tr>
<tr>
<td>Normetanephrine, Free</td>
<td>nmol/L</td>
<td>3.4 (H) . . .</td>
<td>(NL &lt; 0.45)</td>
</tr>
<tr>
<td>Metanephrine, Free, Plasma</td>
<td></td>
<td>0.76 (H) . . .</td>
<td>(NL &lt; 0.9)</td>
</tr>
<tr>
<td>Noradrenaline, Urine</td>
<td>ug/d</td>
<td>73 . . .</td>
<td>(NL &lt; 80)</td>
</tr>
<tr>
<td>Adrenaline, Urine</td>
<td></td>
<td>7.3 . . .</td>
<td>(NL &lt; 20)</td>
</tr>
<tr>
<td>Dopamine, Urine</td>
<td></td>
<td>184 . . .</td>
<td>(NL &lt; 400)</td>
</tr>
<tr>
<td>Metanephrine, Urine</td>
<td></td>
<td>229 . . .</td>
<td>(NL &lt; 400)</td>
</tr>
<tr>
<td>Normetanephrine, Urine</td>
<td></td>
<td>876 . . .</td>
<td>(NL &lt; 900)</td>
</tr>
<tr>
<td>Metanephrines, Total, Urine</td>
<td></td>
<td>1105 . . .</td>
<td>(NL &lt; 1300)</td>
</tr>
</tbody>
</table>
She was given the diagnosis of metastatic pheochromocytoma—location unknown

- Review of prior CT scan showed the liver lesions were old and unchanged

Pt referred to Oncology and Endocrinology (me) for further therapy

MI BG vs PET - ?
IMPRESSION: Status post left adrenalectomy. Focal increased activity within the right adrenal gland could represent normal physiologic activity versus pheochromocytoma with appropriate clinical setting.
Does the patient have pheo or not? If so, where is it?

<table>
<thead>
<tr>
<th></th>
<th>8/25/11</th>
<th>9/1/11</th>
<th>11/15/11</th>
<th>2/9/12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normetanephrine (&lt;0.9) nmol/L</td>
<td>3.4</td>
<td>0.77</td>
<td>1.1</td>
<td>0.72</td>
</tr>
<tr>
<td>Metanephrine (&lt;0.45) &quot;</td>
<td>0.76</td>
<td>0.33</td>
<td>0.37</td>
<td>0.30</td>
</tr>
</tbody>
</table>

- Biochemistry unconvincing (probably negative)
- Imaging fails to localize tumor
- No Pheo
Disorders that may increase both plasma and urinary catecholamines metabolites to levels often seen in 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

As far as we know, none of these was applicable. However, labetolol itself may cause falsely elevated catecholamine/metanephrine measurement.

“...Our studies indicate that labetolol produced a false elevation of urinary catecholamine levels. Although labetolol also interfered with the measurement of urinary excretion of metanephrine, it did not interfere with the measurement of urinary excretion of vanillylmandelic acid, homovanillic acid, 5-hydroxyindoleacetic acid, and serotonin, and it probably did not interfere with the measurement of plasma concentrations of dopamine, norepinephrine, and epinephrine. “

Feldman *J Clin Pharmacol A, 1987 vol. 27 no. 4 288-292*

Labetolol can cause both mild increases in levels (through blockade) and error in measurement.
- Likely exacerbated by IV infusion
The single best test likely depends on the level of suspicion
- Performing test correctly enhances accuracy
  - 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)

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

- 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