40 y/o F with headaches and panic attacks

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Disclosures:

I do not have any relevant financial relationships with any commercial interests.
CC/HPI

40 y/o F presents to the ED with complaints of episodic headaches, palpitations, diaphoresis and chest pain.

Episodes last 20 mins

Episodes occurred for years and are now becoming more frequent (multiple times during the day)

States that her BP varies widely during the day (anywhere 98-200 / 67 -110)
HPI continued

Symptoms started 4 months prior, after the preterm birth of her baby

- PPROM at 30 weeks followed by an emergent C-section
- Baby passed away Day 2 (unclear cause)
4 months ago...

Day # 11 s/p C-section:
- presented to ED with HTN urgency
- SBP 210 -260/ DBP 111-113

Dx with post-partum preeclampsia

Prescribed Procardia 30 mg daily -> increased to 60 mg daily prior to discharge

Prior to discharge had another episode of HTN urgency treated with IV hydralazine

24-hour urine metanephrines sent...
## Labs

<table>
<thead>
<tr>
<th>Test</th>
<th>Ref. Range</th>
<th>8/31/17</th>
<th>Result x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>24-hr Urine studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metanephrines</td>
<td>30-180 normotensive&lt;br&gt;&lt; 400 hypertensive</td>
<td>5546</td>
<td>13.9</td>
</tr>
<tr>
<td>Normetanephrines</td>
<td>119-451 normotensive&lt;br&gt;&lt; 900 hypertensive</td>
<td>29326</td>
<td>32.6</td>
</tr>
<tr>
<td>Total metanephrines</td>
<td>156-561 normotensive&lt;br&gt;&lt; 1300 hypertensive</td>
<td>34872</td>
<td>26.8</td>
</tr>
</tbody>
</table>
Diagnostic testing for Pheochromocytoma

24 hr urine fractionated metanephrines and plasma free metanephrines have > 90% sensitivity

Endocrine society suggests use of either

Plasma tests have a higher specificity (79-98% vs 69- 95%)

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma</td>
<td>Urine</td>
</tr>
<tr>
<td>Lenders, 2002</td>
<td>98.6% (211/214)</td>
<td>97.1% (102/105)</td>
</tr>
<tr>
<td>Unger, 2006</td>
<td>95.8% (23/24)</td>
<td>93.3% (14/15)</td>
</tr>
<tr>
<td>Hickman, 2009</td>
<td>100.0% (14/14)</td>
<td>85.7% (12/14)</td>
</tr>
<tr>
<td>Grouzmann, 2010</td>
<td>95.7% (44/46)</td>
<td>95.0% (38/40)</td>
</tr>
<tr>
<td>Unger, 2012</td>
<td>89.5% (17/19)</td>
<td>92.9% (13/14)</td>
</tr>
</tbody>
</table>
What can cause false positive tests?

Medications can interfere with screening causing a high false positive rate

- Acetaminophen, several classes of antidepressants, stimulants (e.g., ADHD meds)
- Dopamine agonists, Beta blockers, sympathomimetic, opioids, glucocorticoids
- Sympathetic adrenergic overdrive (severe illness, non-supine posture)
- Severe renal insufficiency

**Table 3. Recommendations for Biochemical Testing Conditions**

<table>
<thead>
<tr>
<th>Patient preparation</th>
<th>Avoid sympathomimetic agents (including ephedrine, amphetamine, nicotine)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avoid interfering medication (including labetalol, sotalol, acetaminophen, methyldopa, antidepressants)</td>
</tr>
<tr>
<td></td>
<td>Overnight fast, no caffeinated or decaffeinated beverages</td>
</tr>
<tr>
<td>Conditions for blood sampling of metanephrines</td>
<td>Supine condition, after 30 min of rest</td>
</tr>
<tr>
<td></td>
<td>Collection in heparinized tubes on ice</td>
</tr>
<tr>
<td></td>
<td>Storage of plasma in freezer at $-200^\circ C$ if measured within 3 mo</td>
</tr>
<tr>
<td>Conditions for urine sampling of metanephrines</td>
<td>Collection in container without additives or eventually only sodium bisulfite</td>
</tr>
<tr>
<td></td>
<td>Storage of urine container in a cold place</td>
</tr>
<tr>
<td></td>
<td>Acidify urine in the laboratory to pH 4 before storing</td>
</tr>
</tbody>
</table>
Catecholamine Biosynthesis & Metabolism
Clinical suspicion of pheochromocytoma

Plasma-free (or urinary fractionated) metanephrines

- Normal
  - Tumor highly unlikely
- Either or both metabolites elevated
  - Consider extent of elevation

- Slight to moderate (<3-4X URL)
  - Tumor possible
- Large (>3-4X URL)
  - Tumor highly probable

Stop interfering medications as causes of false-positive test results

Repeat plasma-free (or urinary) metanephrines

- Normal
  - Tumor unlikely
- Metanephrines remain elevated
  - Tumor remains possible

Clonidine suppression test

- Suppression of NMN
  - Tumor unlikely
- No suppression of NMN
  - Tumor highly probable

Locate tumor with imaging studies

Figure 1. Algorithm for biochemical testing.
Per documentation

‘...given the result is not a concerning level for her especially given inpatient admission after emergent surgery and hx of hydralazine administration during her admission. No need to see her in clinic. She should be seen in 3 weeks by PCP and have a random serum methanephrines and normetanephrines drawn. If elevated 2-3 fold higher than the upper limit of normal, she should be seen in hypertension clinic...’
<table>
<thead>
<tr>
<th>Plasma studies</th>
<th>Ref. Range</th>
<th>9/26/17</th>
<th>Result x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (pg/mL)</td>
<td>70-750 (supine)</td>
<td></td>
<td>997</td>
</tr>
<tr>
<td></td>
<td>200-1700 (standing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine (pg/mL)</td>
<td>&lt; 111 (supine)</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>&lt; 141 (standing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine (pg/mL)</td>
<td>&lt; 30</td>
<td></td>
<td>&lt; 25</td>
</tr>
<tr>
<td>Normetanephrine (mmol/L)</td>
<td>&lt; 0.9</td>
<td></td>
<td>53X 58</td>
</tr>
<tr>
<td>Metanephrine (nmol/L)</td>
<td>&lt; 0.5</td>
<td></td>
<td>5.3X 10.6</td>
</tr>
</tbody>
</table>
PCC/PGG syndromes

Significance:
- Catecholamine excess
  - Cardiovascular symptoms/disease
  - Psychiatric symps/disease
  -- Malignancy (10-13%)
- Associated syndromes (Genetic syndromes eg NF1 VHL MEN1)
- Prognosis/Surveillance implications for the patients and their families
Fast forward 4 months later...

Paged overnight

ED physician wanted to discuss the patient. Seen by outpatient Endocrinologist at OSH. Given her symptoms suggested to come to ED. Here vitals are stable, she had mild chest pain that resolved a few hours ago, stable, eating a sandwich. No EKG changes. Trops neg x 2.

What should be the next step?
PMH/PSH:
Asthma
HTN
C-section

Allergies: iodinated contrast - Hives

Medications:
Procardia XL 60 mg daily
Albuterol inhaler prn

Social hx: lives with fiancé, non-smoker, no alcohol, no OTC medications or recreational drugs. Plans to get married in 8 months.
Family hx

Father died (stabbed) when she was 8 yrs old; she is not in touch with father’s family.

Mother has diabetes.

MGM: anxiety attacks, T2DM

M uncle: elevated BP

She has one brother who she believes is healthy.
ROS

Constitutional: No fever. Appetite normal, no fatigue.

HENT: No changes in hearing. No sore throat.

Eyes: No changes in vision

Respiratory: No cough, + mild palpitations, + intermittent shortness of breath

Cardiovascular: + chest pain, no orthopnea.

Gastrointestinal: + nausea, + vomiting, no diarrhea, no constipation. No blood in the stool.

Genitourinary: No dysuria or hematuria.

Skin: no new rashes.

Neurological: No weakness, + intermittent headaches.

Musculoskeletal: No swelling.

Endo: No chills or hot flashes.

Heme: No easy bruising.
11/18/2017

Glucose: 483 (H)
Sodium: 132 (L)
Potassium: 3.6
Chloride: 95
Carbon Dioxide: 21 (L)
Anion Gap: 16 (H)
BUN: 9
Creatinine: 0.8
GFR Estimate (Calc): 79
Calcium: 10.0

Beta-Hydroxybutyrate 0.10
HbA1c: 10.9
Suggested

Patient has classic history and biochemically proven pheochromocytoma

What would be the next step in management?
Imaging with CT scan Abd – to localize the lesion
CT Abd/pelvis

7.9 x 6.1 cm L suprarenal mass concerning for pheochromocytoma
Historical Overview: Pheochromocytoma

Mid 1800s – 1st description of the 2 distinct layers of the adrenal gland (cortex & medulla), recognized in patients who died with adrenal destruction secondary to tuberculosis.

1912: Ludwig Pick described pheochromocytoma
   Greek, meaning “dusky-colored tumor”
   He noted the dark-brown color of the cells with contact with chrome salts

1926-1927: 1st surgical removal of pheochromocytoma in Europe was performed in 1926 and by Mayo in USA in 1927.
Pheochromocytoma/Paraganglioma (PGG)

80-85% arise from adrenal medullary chromaffin tissues

15-20% extra-adrenal sympathetic derived chromaffin tissues

- Abdomen > pelvis >> rarely mediastinum
- Head & neck PGG = mostly dopamine secreting
Pheochromocytoma/Paragangliomas

Rare but devastating/fatal consequences if not recognized
- Autopsy studies: substantial # undiagnosed

25% of PCC/PGG are malignant
25% are extra-adrenal

40% hereditary
- pediatric patients = 80% hereditary

No cure for widely metastatic disease (only 50% 5 year survival)
All patients will need life long screening
Challenges

Symptoms of catecholamine hypersecretion unrecognized as the mimic other conditions

Extra-adrenal gland tumors require more widespread imaging

Mortality:
- Few decades ago: 30 – 45%.
- Now: 0-2.9%
Perioperative blockade

The purpose to block to peripheral effects of catecholamines to minimize excessive intra operative adrenergic receptor agonism that may result in end organ damage, while simultaneously reducing the risk of post op hypotension.

Experienced surgery/ anesthesia team

Usually admitted the day prior, IV fluids, oral salt given to expand the blood volume to prevent pre op orthostatic hypotension and post op hypotension

Post op: Screened with plasma metanephrines 4-8 weeks post surgery to ensure complete resection and then annually
**Pre op management**

Endocrine Society suggests:

- Phenoxybenzamine as 1\(^{st}\) line treatment (non selective non competitive alpha blocker)
- Doxazosin or another competitive selective alpha-blocker +/- calcium channel blocker as 2\(^{nd}\) line treatment
Metastatic disease

Presence of distant mets in non chromaffin tissue

Risk factors:
- SDHB mutation
- Tumor size ( > 4-5 cm)
- Secretion of methoxytyramine
- Life-long screening
123 I – MIBG is useful to determine the avidity of the metastatic disease in prep for possible future 131I – MIBG treatment

F- FDG- PET /CT recommended for Succinate Dehydrogenase Subunit (SDHB) mutation ( pt population 74- 100% sensitive to PET scans)
Management of metastatic disease

Treatments are not curative
- Debulking surgery
- Chemotherapy with cyclophosphamide, vincristine and dacarbazine (CVD)
- External beam radiation
- 131- MIBG treatment
- Tyrosine kinase inhibitors tested in clinical trials
A Phase II Study Evaluating the Efficacy and Safety of Ultratrace Iobenguane I 131 in Patients With Malignant Relapsed/Refractory Pheochromocytoma/Paraganglioma

Designed to evaluate the effectiveness and collect additional safety information on AZEDRA® (iobenguane I 131) for the treatment of metastatic or relapsed/refractory or unresectable PCP or PGG

This Phase II study will help determine

- Primarily if using the drug reduces the amount of blood pressure medication being taken as a result of the cancer

- Secondarily to determine effectiveness of the study drug, additional safety measures, and to assess if the drug helps the quality of life and use of pain medication.

All subjects will receive an imaging dose with scans followed by two therapeutic doses given approximately 3 months apart.
Should this patient have genetic testing?

Endocrine Society suggests all pts should be engaged in shared decision making regarding genetic testing.
### Genetics

13 known susceptible genes, most inherited in AD pattern

SDHD and SDHAF2 have paternal inheritance, SDHB highest penetrance, 80% malignancy risk

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Protein (Function)</th>
<th>Tumor Location</th>
<th>Malignancy Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF1</td>
<td>Neurofibromatosis Type 1</td>
<td>Neurofibromin (GTPase which inactivates RAS)</td>
<td>Adrenal (bilateral)</td>
<td>12%</td>
</tr>
<tr>
<td>RET</td>
<td>Multiple Endocrine Neoplasia Type 2</td>
<td>RET (transmembrane tyrosine kinase)</td>
<td>Adrenal (bilateral)</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>VHL</td>
<td>von Hippel Lindau</td>
<td>pVHL (ubiquitin ligase activity)</td>
<td>Adrenal (bilateral)</td>
<td>5%</td>
</tr>
<tr>
<td>SDHx genes</td>
<td>Familial paraganglioma syndrome</td>
<td>Succinate dehydrogenase complex (complex II of the mitochondrial respiratory chain and converts succinate to fumarate)</td>
<td>Any location</td>
<td>Low</td>
</tr>
<tr>
<td>SDHA</td>
<td></td>
<td>SDH subunit A (catalytic subunit)</td>
<td>Any location, primarily extra adrenal</td>
<td>23%</td>
</tr>
<tr>
<td>SDHB</td>
<td></td>
<td>SDH subunit B (catalytic subunit)</td>
<td>Head and neck, can be thoracic</td>
<td>Low</td>
</tr>
<tr>
<td>SDHC</td>
<td></td>
<td>SDH subunit C (anchoring subunit)</td>
<td>Any location, primarily head and neck</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>SDHD</td>
<td></td>
<td>SDH subunit D (anchoring subunit)</td>
<td>Head and neck (multifocal)</td>
<td>Low</td>
</tr>
<tr>
<td>SDHAF2 (SHD5)</td>
<td></td>
<td>SDH cofactor AF2 (cofactor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMEM127</td>
<td>Transmembrane protein 127</td>
<td>Transmembrane protein 127 (transmembrane protein)</td>
<td>Any location, primarily adrenal</td>
<td>Low</td>
</tr>
<tr>
<td>MAX</td>
<td>MYC-associated protein X</td>
<td>MYC-associated protein X (transcription factor)</td>
<td>Adrenal (bilateral)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>EPAS1</td>
<td>Polycythemia paraganglioma syndrome</td>
<td>Hypoxia inducible factor 2a (transcription factor)</td>
<td>Any location</td>
<td>Not known</td>
</tr>
<tr>
<td>FH</td>
<td>Hereditary leiomyomatosis and renal cell carcinoma</td>
<td>Fumarate hydratase (converts fumarate to malate)</td>
<td>Any location</td>
<td>Possibly high</td>
</tr>
<tr>
<td>MDH2</td>
<td></td>
<td>Malate dehydrogenase (converts malate to oxaloacetate)</td>
<td>Any location</td>
<td>Not known</td>
</tr>
</tbody>
</table>
Follow-up

Started on doxazosin starting at 1 mg in PM and 2 mg in AM and titrated up PRN

Endocrine surgery:
- Seen in clinic
- Plan for laparoscopic left adrenalectomy
- Possibility of having to convert to an open operation is ~15-20%
Take away points

Most common false positives are due to interfering medicine or drugs
Perioperative management is important for successful surgical outcomes
Up to 40% of pts have germline mutation; all patients with PCP/PGG should be referred to a genetic counsellor irrespective of their family history
References


