“NO TUMOR, YET SYMPTOMS”

PHEOPARA ALLIANCE WEBINAR
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DISCLOSURES

No financial disclosures related to this talk
OBJECTIVES

• 1. Consider the evaluation of persistent symptoms of pheochromocytoma, yet no tumor.

• 2. Treatment options?
CASE 1

• 60 year-old male had a head and neck PGL with an unknown pathogenic variant
• Operated and PGL was removed
• Afterwards:
  • Swings in blood pressures
  • Catecholamines and imaging negative!!
• What’s going on?
SIGNS AND SYMPTOMS OF PHEOCHROMOCYTOMA

• Nervousness/anxiety,
• Flushing,
• Profuse sweating,
• Palpitations,
• Headache
• Less common manifestations may include chest pain, nausea, vomiting, dizziness, paleness.

Tevosian and Ghayee, Endocrinol Metab Clin North Am. 2019
# PLASMA AND URINARY METANEPHRINES

<table>
<thead>
<tr>
<th>First Author, Year (Ref.)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma</td>
<td>Urine</td>
</tr>
<tr>
<td>Lenders, 2002 (39)</td>
<td>98.6% (211/214)</td>
<td>97.1% (102/105)</td>
</tr>
<tr>
<td>Unger, 2006 (42)</td>
<td>95.8% (23/24)</td>
<td>93.3% (14/15)</td>
</tr>
<tr>
<td>Hickman, 2009 (46)*</td>
<td>100.0% (14/14)</td>
<td>85.7% (12/14)</td>
</tr>
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<td>Grouzmann, 2010 (48)</td>
<td>95.7% (44/46)</td>
<td>95.0% (38/40)</td>
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<tr>
<td>Unger, 2012 (53)</td>
<td>89.5% (17/19)</td>
<td>92.9% (13/14)</td>
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* Data restricted to that available from Table 4 of those studies where all measurements were made.

Lenders, JCEM, 2014
Beware of Medications Causing False Positive Results!!

Table 2
Medications often responsible for false positive results in PCC/PGL diagnosis

<table>
<thead>
<tr>
<th>Medication</th>
<th>High Metabolite Level (False Positive Result for PCC/PGL diagnoses)</th>
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<tbody>
<tr>
<td>α-Blockers</td>
<td>Norepinephrine, normetanephrine</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Norepinephrine, epinephrine</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Norepinephrine, epinephrine</td>
</tr>
<tr>
<td>Levodopa</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td>MAO inhibitors</td>
<td>Normetanephrine, metanephrine</td>
</tr>
<tr>
<td>Sympathomimetics (ephedrine, albuterol, amphetamines)</td>
<td>Norepinephrine, epinephrine, Normetanephrine, metanephrine</td>
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<tr>
<td>Tricyclic antidepressants</td>
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STILL PERSISTENT SIGNS AND SYMPTOMS!

• Recurrence?
  • Pathogenic variants- SDHB, HIF2-alpha, ATRX, FH, MAX, MAML3

• However, our patient doesn’t have any of these pathogenic variants!

• Note- if metanephrines are negative, and there is **NO tumor** on imaging, **symptoms are less likely related** to pheochromocytoma as they continuously release hormones where stable breakdown products can be measured.

Tevosian and Ghayee, Endocrinol Metab Clin North Am. 2019
ANOTHER DIAGNOSIS?
ANOTHER DIAGNOSIS?

- Differential diagnosis:
  - Kidney related high blood pressure?
    - If $SDHx$ pathogenic variant, some patients can get kidney cancer, so blood pressures can increase - but NO erratic symptoms like pheochromocytoma.

Mamilla, Pacak, Endocrinol Metab Clin N Am, 2019
Mastocytosis is a rare disorder characterized by abnormal accumulation and activation of immune cells in the skin, bone marrow and internal organs.

• Skin lesions?
• Flushing?
• Itching?
• Diarrhea?
Due to hormones that cause:
- Flushing,
- Fast heartbeat,
- Difficulty breathing
- Diarrhea
THYROID?

• Hyperthyroidism:
  • Fast heartbeat
  • Nervousness
  • Tremor
  • Sweating

Endocrine Society; Smith and Hegedus, NEJM, 2016
Postural: Related to the position of your body.
Orthostatic: Related to standing upright.
Tachycardia: A heart rate over 100 beats per minute.
Syndrome: A group of symptoms that happen together.

Not able to coordinate the balancing act of blood vessel constriction (squeezing) and heart rate response.
• Higher risk of developing POTS after experiencing the following stressors:
  • Significant illnesses, such as viral illnesses like mononucleosis or serious infections.
  • Pregnancy.
  • Physical trauma, such as a head injury.
  • Surgery.
PSEUDOPHEEOCHROMOCYTOMA?
(PSEUDOPHEEO)
WHAT IS PSEUDOPHEO?

• Clinical presentations of PSEUDOPHEO are similar to that of PHEO:
  
  • Recurrent peaks in blood pressure, however, showing no anatomical and biochemical abnormality
    
    • altered function of the autonomic nervous system or abnormal disposition of catecholamines released from neurons within the brain.
  
  • Absence of an adrenal tumor on imaging studies are useful to delineate PSEUDOPHEO from a typical PHEO.
Stimulation of a neural limb causes an increased norepinephrine release.

Stimulation of an adrenal limb causes an increased epinephrine release causing increased heart rate.

Mamilla, Pacak, Endocrinol Metab Clin N Am, 2019
PSEUDOPHEO

- Unknown etiology,
- Unidentified pathophysiological mechanisms,
- Often amplified cardiovascular responses utilizing antihypertensive medications.
- Diagnosis of exclusion

Mann SJ. Severe paroxysmal hypertension, 1996
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<th>Other differentials</th>
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<td><strong>Baroreceptor failure is due to:</strong> accidental injury, neck surgery, or irradiation and is associated with both hypertension and hypotension</td>
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CASE 1

• 60 year-old male had a head and neck PGL with *SDHD* pathogenic variant

• Operated on neck PGL

• No tumor

• Swings in blood pressures

• Catecholamines and imaging negative!!

• What’s going on?
Functions of the Baroreceptors

- Maintains relatively constant pressure despite changes in body posture.

Supine → Standing

↑ Sympathetic Nervous Activity

Vasomotor Center

Sensed By Baroreceptors

Decrease Central Blood Volume

Decrease Cardiac Output

Decrease Arterial Pressure
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- **PseudoPHEO - No injury or neck surgery**

- **PseudoPHEO - Not triggered**

- **Baroreceptor failure**
  - Caused by accidental injury, neck surgery, or irradiation
  - Associated with both hypertension and hypotension

- **Labile High Blood Pressure**
  - Can be triggered by salt, alcohol, drugs, other medical conditions
  - Patients are aware of the fact that their blood pressure is elevated, for example, when they are stressed.

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<td>PseudoPHEO – No traumatic event</td>
<td><strong>Post traumatic stress disorder-</strong> Traumatic event causes changes in catecholamines causing symptoms</td>
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CASE 2

• 37 year-old male presents to emergency room with hypertensive urgency

• Blood pressures: 190/100 mmHg

• Heart rate 105 beats per minute

• He had a history of pheochromocytoma surgically removed 1 year ago. Biochemical work-up from 6 months ago was normal.
CASE 2

- He has symptoms of headaches, palpitations often and on.
  - Occasional spikes in blood pressures 2-3 times a month
  - Other history: in the last year has been having more allergies
- No known genetic mutations
- Repeat biochemical evaluation showed normal metanephrines
- CT scan showed thickness in the left adrenal gland
CASE 2

- Thyroid disease ruled out
- Mastocytosis ruled out
- Carcinoid ruled out
- Vasculitis ruled out
- Further history: recent anxiety due to job related issues. Worried about next meal, had been drinking more caffeinated beverages to stay up and finish work.
MANAGEMENT

• Depends on the underlying diagnosis
• Possible management of symptoms with blood pressure medications
  • Different classes of medications tend to be helpful:
    • Calcium channel blockers
    • β-blockers
    • α-blockers
PREVENTIVE MEASURES

In specific cases:

- Antidepressants in consultation with a psychologist/psychiatrist helpful in certain cases of increased anxiety and depression
- Address repressed emotions regarding their disease state

A well tolerated approach would be a combination of α-adrenoceptor blocker and β-adrenoceptor blockers
CONCLUSIONS

• If the work-up for recurrence is negative, these symptoms are not imaginary as they can exist.

• If metanephrines are negative, and there is NO tumor on imaging, symptoms are less likely related to pheochromocytoma as they continuously release hormones where stable breakdown products can be measured.
CONCLUSIONS

• If no tumor is found a differential diagnosis should be considered.

• Symptomatic treatment with $\alpha$, $\beta$, or calcium channel blockers can be helpful in selective patients.

• As these symptoms can be challenging, continue to follow with healthcare team.

Mamilla, Pacak, Endocrinol Metab Clin N Am, 2019; World Health Organization
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- Leon Moreno, MD

University of Florida Genetics – Lisa A. Brown

University of Florida Radiation Oncology
- Kathryn Hitchcock, MD

Our patients & their families

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THANK YOU!