

Approach to a patient with a possible pheochromocytoma (PHEO)

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Disclosure

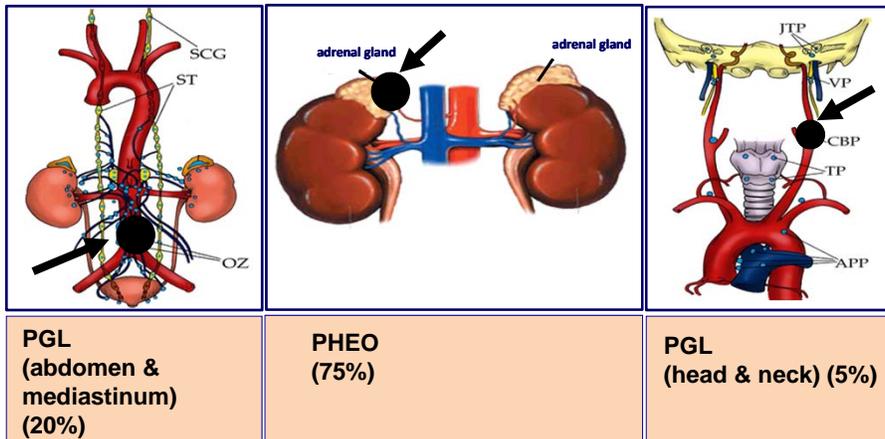
Nothing to disclose

Objectives

After this lecture, participants should be able to:

1. Perform appropriate biochemical tests to identify a patient with PHEO
2. Identify imaging techniques to properly localize PHEO
3. Identify drugs affecting catecholamine metabolism

PHEO: Definition/Background



PGL: extra-adrenal PHEO

OZ: the organ of Zuckerkandl; CBP: carotid body PGL

CASE

A 22 y.o. old white female presented to an endocrinologist with a h/o intermittent headaches and abdominal pain (RUQ). She c/o having episodes of palpitations, sweating and pallor 2-3x/week. She also c/o infrequent episodes of cough and chest tightness along with constipation.

Her past medical history was positive for a high blood pressure (141/89) at age 18; irregular menses; the patient is obese with a possible diagnosis of anxiety/depression as she is currently on Venlafaxine (Effexor) 100 mg QD.

Family history:

Father: 52 y.o.: history of a neck tumor?

Mother: 49 y.o.: healthy

CASE

On physical examination, the patient was found to be obese and anxious; she had mild hirsutism and visible facial sweating during the exam.

BP: 137/92, HR: 95; Temp. 36.7; RR:17

Working diagnosis:

1. Possible PCOS
2. Anxiety/depression
3. Tachycardia secondary to anxiety or another etiology
4. Hypertension

An endocrinologist decided to prescribe atenolol 25 mg BID.

CASE

Three days after, the patient suddenly developed a very severe headache followed by nausea, visual problems, palpitations, and frequent sweating.

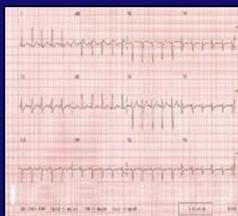
The patient presented to the nearest ER where she was found to be under moderate distress; her BP: 205/115; HR: 78, RR: 20.

Could this be PHEO and, if so, what went wrong initially?

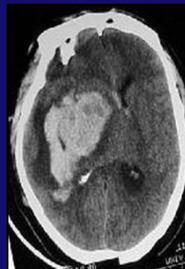
PHEO as a volcano



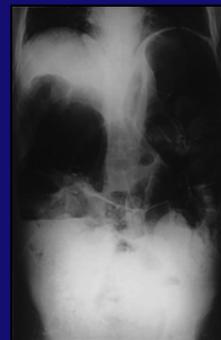
The concentrations of catecholamines in PHEO tissue are enormous (more than a billion times higher than in plasma), creating a volcano that can erupt at any time (episodes are called storms, attacks, or spells).



Sinus tachycardia



Large intracerebral hemorrhage



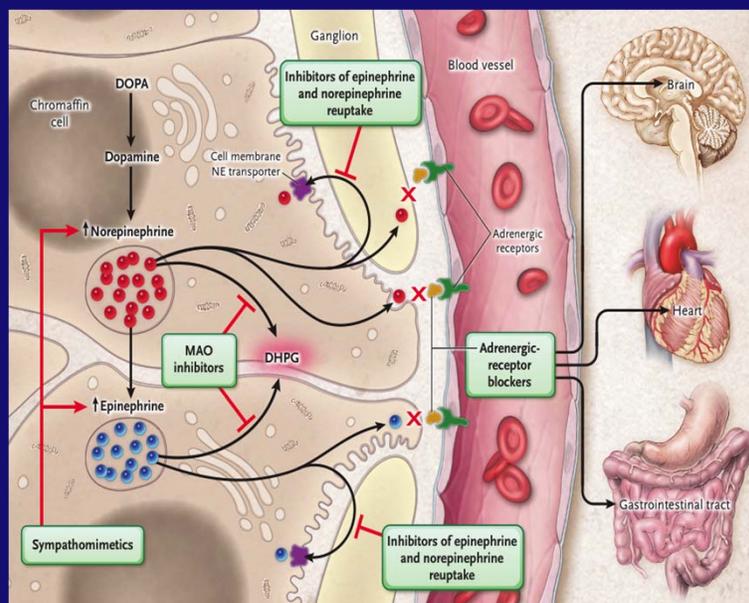
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PHEO/PGL as a volcano

Practically all patients with biochemically positive PHEO should be treated by alpha/beta adrenoceptor blockers to prevent any cardiovascular complications.

An exception could be patients with biochemically negative or dopamine/methoxytyramine-secreting PHEO.

PHEO: Drug effects on catecholamines



Pacak & Neary NEJM 2011; 364:2268

Main drugs contraindicated in PHEO

TABLE 3. Main classes of drugs with contraindications in patients with pheochromocytoma

Drug class	Relevant clinical uses
β -Adrenergic blockers ^a	May be used to treat conditions that result from catecholamine excess (e.g. hypertension, cardiomyopathy, heart failure, panic attacks, migraine, tachycardia and cardiac dysrhythmias)
Dopamine D ₂ receptor antagonists	Control of nausea, vomiting, psychosis, hot flashes and for tranquilizing effect
Tricyclic antidepressants	Treatment of insomnia, neuropathic pain, nocturnal enuresis in children, headaches, depression (rarely)
Other antidepressants (serotonin and NE reuptake inhibitors)	Depression, anxiety, panic attacks, antiobesity agents
Monoamine oxidase inhibitors	Non-selective agents rarely used as antidepressants (due to "cheese effect").
Sympathomimetics ^a	Control of low blood pressure during surgical anesthesia; decongestants; antiobesity agents
Chemotherapeutic agents ^a	Antineoplastic actions; treatment of malignant pheochromocytoma
Opiate analgesics ^a	Induction of surgical anesthesia
Neuromuscular blocking agents ^a	Induction of surgical anesthesia
Peptide and steroid hormones ^a	Diagnostic testing

Adapted from Eisenhofer *et al.* (76).
^a These drugs have therapeutic or diagnostic use in pheochromocytoma, but usually only after pretreatment with appropriate antihypertensives (e.g. α -adrenoceptor blockers).

CASE

How should the patient be treated now?

1. Add an alpha adrenoceptor blocker
2. Add an ACE inhibitor
3. Stop atenolol

Answer: 1

CASE

An alpha adrenoceptor blocker (doxazosin 2 mg QD) was initiated and the patient's BP was found to be 135/82.

CASE

What would be the next step in the diagnosis or management of a possible PHEO?

1. Use another antidepressant
2. Biochemical testing and/or imaging
3. Observation

Answer: 2

CASE

Plasma tests revealed:

NE: 2679 pg/ml (< 750)

NMN: 370 pg/ml (< 112)

EPI: 42 pg/ml (< 51)

MN: 55 pg/ml (< 61)

An abdominal CT was ordered and revealed a 2.0 cm mass in the right adrenal gland with HU around 8.

CASE

What would be the next step in the diagnosis or management of a possible right adrenal PHEO?

1. Operate on the patient to remove adrenal PHEO
2. Additional testing or imaging
3. Observation

Answer: 2

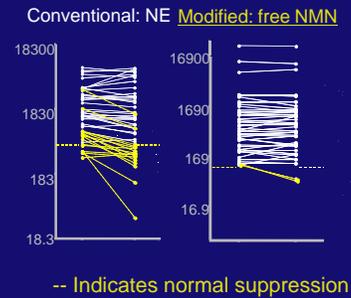
Equivocal biochemical test results

- Results between upper reference limit (URL) and 4x above URL

Grey zone

Clonidine test: Distinguishes increased sympathetic activity (false-positives) from PHEO (true-positives).

- Introduced **clonidine test coupled** with the measurement of plasma normetanephrine (NMN; sens. 97% /vs 60% for NE/; spec. 100%)



Eisenhofer et al. JCEM 2003; 88:2656
Eisenhofer et al. JCEM 2010; 95:238
Pacak et al. NEJM 2011; 364:2268

CASE

Results from the clonidine suppression test:

Plasma catecholamines and metanephrines:

Before:

NE: 2500
NMN: 360

After:

NE: 1340 (47% decrease)
NMN: 252 (30% decrease)

CASE

What would be the next step in the diagnosis or management of a possible right adrenal PHEO?

1. Operate on the patient to remove adrenal PHEO
2. Additional biochemical testing or imaging
3. Observation

No answer to be given, the audience to decide

Discussion

The patient was operated and the right adrenal tumor was removed. Histopathology revealed adrenal adenoma; no PHEO was found.

After the operation, the patient was still presenting with high BP, tachycardia, and sweating.

Plasma tests now show:

NE: 2345 pg/ml (< 750)

NMN: 390 pg/ml (< 112)

EPI: 29 pg/ml (< 51)

MN: 52 pg/ml (< 61)

CASE

What would be the next step in the diagnosis or management of a possible PHEO?

1. Change antidepressant medication and observe
2. Additional biochemical or imaging testing
3. Re-review pathology findings (2nd opinion)

Answer: 2

Discussion

The patient underwent a whole body CT scan and was found to have a 3.5 cm mediastinal mass (HU 47). MRI confirmed the mass and showed a hyperintense T2 image.

¹²³I-MIBG scintigraphy confirmed the mass in the mediastinum.

CASE

What would be the next step in the diagnosis or management of a possible extra-adrenal PHEO?

1. Removal of a mass in the mediastinum
2. Additional biochemical testing or imaging
3. Observation

Answer: 1

Teaching points

1. Carefully examine biochemical results:

- PHEO: most produce EPI/MN; 99% of EPI is derived from the adrenal glands
- If an adrenal mass is found and EPI/MN is elevated 4x above the URL, it is almost always an adrenal PHEO EXCEPT when:
 - a patient is taking antidepressants that can elevate catecholamines/metanephrines 3-4x above the URL: stop medication and/or repeat biochemical testing

Teaching points

- If an adrenal mass is found and NE/NMN is elevated 4x above the URL – be careful to conclude that an adrenal mass is PHEO:
 - Adrenal adenomas are very common and have HU less than 10 on CT (almost never for PHEO)
 - NE/NMN is mainly derived from chromaffin cells & sympathetic nervous system outside the adrenal gland

Teaching points

2. After any drugs are considered and stopped (note that often antidepressants or antihypertensives cannot be stopped) but biochemistry is still positive perform the clonidine suppression test.
 - This test is valid only in patients with elevated NE and/or NMN
 - The test is positive if NE decreases less than 50% from its baseline value but not below the URL (NMN: 40% or not below the URL)

Teaching points

3. If the clonidine test is positive, perform imaging using abdominal CT or MRI first.
 - An abdominal mass is detected on CT: if HU < 10, it is almost never PHEO; do NOT be fooled by the detection of a mass; if low HU and MRI does not show a hyperintense focus, PHEO is excluded.....
 - Search further for a PHEO in other locations.... whole body CT is needed

Teaching points

4. Confirm results from CT/MRI using PHEO-specific functional imaging modality
 - ^{123}I -MIBG scintigraphy
 - ^{18}F -fluorodopamine; ^{18}F -fluorodopa PET/CT

Teaching points

5. Do not ever put a patient in whom you suspect PHEO on beta adrenoceptor blockers first.
6. Remember that antidepressants may cause elevation of plasma catecholamines/metanephrines resembling the presence of PHEO.