As a VHL patient, what you need to know about pheochromocytoma (PHEO)

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PHEOs are neuroendocrine (chromaffin cell) tumors characterized by catecholamine synthesis, release, and metabolism.

If PHEO is undiagnosed or not properly localized, the tumor can be fatal.

- Lethal arrhythmia
- Myocardial infarction
- Malignant hypertension
- Stroke
Current important facts:

- In over 50% of PHEOs/PGLs, a genetic defect is known (35-40% have germline and 15-25% harbor somatic mutations); 19 PHEO/PGL susceptibility genes are currently known.

- Biochemical dx. and localization are highly successful.

- First clinical practice guideline launched in 2014.

- There is no satisfactory cure for metastatic PHEO/PGL.

- International studies and consortia are evolving.
PHEO: Definition/Background

PGL: extra-adrenal PHEO

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

PHEO

PARAGANGLIOMA (PGL)

Sympathetic

Adrenal

Extra-adrenal

Parasympathetic

Head & Neck
5 major susceptibility genes: *VHL*, *RET*, *SDHB*, *SDHD*, *NF1* now represent about 90% of hereditary PHEOs/PGLs

5 minor susceptibility genes: *SDHA*, *SDHC*, *TMEM127*, *MAX*, *SDHAF2* now represent about 10% of hereditary PHEOs/PGLs

**HIF2A:** PGL & polycythemia (2012).

**H-RAS:** PHEOs in males (2013)

**FH:** PHEO/PGL: multiple (2014)
Von Hippel-Lindau (VHL) syndrome

- PHEO and very rarely PGL
- Up to 25% of patients will develop PHEO
- Up to 50% of patients will have bilateral PHEO
- Always NE producing tumors
Multiple endocrine neoplasia 2 (MEN2)

**MEN2a:**
- RET oncogene (codon 634)
  - a/ PHEO in 50-75% of patients
  - b/ 50% bilateral
  - c/ EPI or EPI & NE tumors
- Hyperparathyroidism
- Medullary thyroid cancer

**MEN2b:**
- Marfanoid habitus
- Multiple neuromas
Neurofibromatosis 1 (NF1)

- PHEO (2-5%): EPI & NE producing tumors
- Neurofibromas (2 or more)
- Optic glioma
- Lisch nodules (iris hamartomas, 2 or more)
- Cafe-au-lait macules (6 or more)
Metanephrines: Normetanephrine (from NE)  
Metanephrine (from EPI)

3rd International Symposium on PHEO (ISP): Initial testing for PHEO should include measurements of fractionated metanephrines in plasma, urine, or both, as available. There was no consensus about plasma versus urine measurements as the preferred test. 4x > URL: almost always PHEO.
Metanephrines as O-methylated metabolites in the biochemical diagnosis of PHEO/PGL

Metanephrines are produced continuously and independently of catecholamine secretion.

<table>
<thead>
<tr>
<th>Biochemical test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children</td>
<td>Adults</td>
</tr>
<tr>
<td>Plasma normetanephrine and metanephrine</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Plasma norepinephrine and epinephrine</td>
<td>92</td>
<td>84</td>
</tr>
<tr>
<td>Urinary normetanephrine and metanephrine</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>Urinary norepinephrine and epinephrine</td>
<td>100</td>
<td>86</td>
</tr>
<tr>
<td>Urinary vanillylmandelic acid</td>
<td>-</td>
<td>64</td>
</tr>
</tbody>
</table>

214 pts with and 600 without PHEO included

Lenders et al. JAMA 2002; 287:1427
Sawka et al. JCEM 2004; 89:2859
Sinus tachycardia
Large intracerebral hemorrhage
Ileus

All patients with PHEO/PGL must receive $\alpha$ ($\beta$) adrenoceptor blockade.

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).
# PHEO: symptoms & signs

<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Hypertension</td>
<td>Headaches</td>
</tr>
<tr>
<td>Sustained hypertension</td>
<td>Palpitations</td>
</tr>
<tr>
<td>Paroxysmal hypertension</td>
<td>Excessive sweating</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>Anxiety/nervousness</td>
</tr>
<tr>
<td>Tachycardia or reflex bradycardia</td>
<td>Tremulousness</td>
</tr>
<tr>
<td>Pallor</td>
<td>Pain in chest/abdomen</td>
</tr>
<tr>
<td>Flushing (rare)</td>
<td>Weakness, fatigue</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Fasting hyperglycaemia</td>
<td>Dizziness or faintness</td>
</tr>
<tr>
<td>Decreased gastrointestinal motility</td>
<td>Paresthesias</td>
</tr>
<tr>
<td>Increased respiratory rate</td>
<td>Constipation (rarely diarrhea)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Visual disturbances</td>
</tr>
</tbody>
</table>

Highest (++++) to lowest (+) frequency
**Treatment**

**Pharmacological blockade**

Alpha: Phenoxybeznamine (usually 10-30 mg TID)

Beta: Atenolol, metoprolol (beta 1), propranolol (beta 1 and 2) (25-50 mg)

Alpha and beta: Labetelol (hypertensive crisis??)

Ca channel blockers: Norvasc (start with 10 mg QD)

Blockade of catecholamine synthesis: Metyrosine (Demser) (usually 250 mg TID).

**Hypertensive crisis**

Phentolamine (Regitine): 5 mg i.v. bolus
Equivocal biochemical test results

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

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

- Introduced modified 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
Methoxytyramine as a novel biomarker of SDHx and metastatic PHEO/PGL

4.7-fold higher in patients with than without metastases; independent of tumor burden and NMN levels
Methoxytyramine in cluster 1 & 2 PHEOs/PGLs

Cluster 1

- **VHL**: NE (8%), SDHB: NE/DA (65%), SDHD: NE/DA (Low), SDHA/C/AF2: NE/DA (Low)

Cluster 2

- **RET**: EPI/NE (<5%), NF1: EPI/NE (8%), TMEM127: EPI/NE (<5%), MAX: NE>EPI (10%)
Kidney failure and plasma metanephrines

Eisenhofer et al. Kidney Int. 2005; 67:668
Biochemical profile points to proper localization and genetic testing.

<table>
<thead>
<tr>
<th>Localization</th>
<th>Genetic test</th>
</tr>
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<tbody>
<tr>
<td>EPI/MN:</td>
<td>ADRENAL MEN; SPOR</td>
</tr>
<tr>
<td>NE/NMN:</td>
<td>ADRENAL VHL, SDHB/D</td>
</tr>
<tr>
<td>NE+EPI/MN+NMN:</td>
<td>ADRENAL MEN; NF-1; SPOR</td>
</tr>
</tbody>
</table>
Tumor size, extra-adrenal location, and SDHB as independent predictors of metastatic PHEO

365 patients with PHEO, including 105 with metastases, 846 subjects without tumor

ADRENAL PHEO

CT/MRI positive

Is functional imaging necessary?
Adrenal PHEO: Biochemical phenotype and tumor size determines functional imaging

Localization Functional imaging

↑ EPI/MN: ADRENAL (less than 5 cm) NO

↑ EPI/MN: ADRENAL (more than 5 cm) YES

↑ NE/NMN: ADRENAL & EXTRA-ADRENAL YES
PHEO/PGL born to be imaged: Cell-specific characteristics for functional imaging

Implementation of functional imaging for hereditary and non-hereditary PHEO/PGL localization

Primary PHEO/PGL

$^{18}$F-FDOPA PET: 67-93%
$^{123}$I-MIBG scinti. (specific): 67-86%
$^{18}$F-FDG PET: 83-93% (adrenal: 67%)

Metastatic PHEO/PGL (per lesion)

$^{18}$F-FDG PET: 74%
Octreoscan: 68%

$^{123}$I-MIBG: 57% (if th. considered)
$^{18}$F-FDOPA PET: 45%
18F-FDOPA and head and neck PGLs

SDHx head and neck PGLs: 18F-FDOPA
100% (9 pts)
PHEO and somatostatin receptors: imaging

- PHEOs express 5 somatostatin receptors (SSTRs) allowing for the use of Octreoscan scintigraphy (relatively poor spatial resolution)

- SSTR imaging can be performed with PET/CT, improving spatial resolution; also provides more rapid and whole-body tomographic imaging for precise anatomic localization

- Available 3 DOTA-coupled peptides include: $^{68}$Ga-DOTATATE, $^{68}$Ga-DOTATOC, $^{68}$Ga-DOTANOC
$^{68}$Ga-DOTA analogs: A future imaging approach?

$[^{68}\text{Ga}]-\text{DOTATATE}$  $[^{18}\text{F}]-\text{FDG}$  $[^{18}\text{F}]-\text{DOPA}$  $[^{18}\text{F}]-\text{FDA}$

$[^{68}\text{Ga}]-\text{DOTATATE}$  $[^{111}\text{In}]-\text{Pentetreotide}$  $[^{123}\text{I}]-\text{MIBG}$

NIH group & Taieb et al.; ongoing studies
Metastatic disease: No curative treatment available.

• Surgical debulking may increase survival and decrease catecholamine burden; but data are not available.

• If a pt is:  + MIBG ----> $^{131}$I-MIBG therapy
  - MIBG ----> chemotherapy

• Chemotherapy: 1st choice in a rapidly progressive tumor!!

Remember: $^{131}$I-MIBG or chemotherapy: only about 1/3 of patients respond (no cure, only a partial response).
### TABLE 3. Main classes of drugs with contraindications in patients with pheochromocytoma

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Relevant clinical uses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Adrenergic blockers</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>May be used to treat conditions that result from catecholamine excess (e.g. hypertension, cardiomyopathy, heart failure, panic attacks, migraine, tachycardia and cardiac dysrhythmias) Control of nausea, vomiting, psychosis, hot flashes and for tranquilizing effect Treatment of insomnia, neuropathic pain, nocturnal enuresis in children, headaches, depression (rarely) Depression, anxiety, panic attacks, antiobesity agents</td>
</tr>
<tr>
<td>Dopamine D2 receptor antagonists</td>
<td></td>
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<tr>
<td>Tricyclic antidepressants</td>
<td></td>
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<tr>
<td>Other antidepressants (serotonin and NE reuptake inhibitors)</td>
<td>Non-selective agents rarely used as antidepressants (due to &quot;cheese effect&quot;). Control of low blood pressure during surgical anesthesia; decongestants; antiobesity agents Antineoplastic actions; treatment of malignant pheochromocytoma Induction of surgical anesthesia Induction of surgical anesthesia Diagnostic testing</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td></td>
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<tr>
<td>Sympathomimetics&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Chemotherapeutic agents&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Opiate analgesics&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular blocking agents&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Peptide and steroid hormones&lt;sup&gt;a&lt;/sup&gt;</td>
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</tbody>
</table>

Adapted from Eisenhofer et al. (76).

<sup>a</sup> These drugs have therapeutic or diagnostic use in pheochromocytoma, but usually only after pretreatment with appropriate antihypertensives (e.g. α-adrenoceptor blockers).
CT contrast: No harm to patients with PHEO/PGL

22 patients studied
Acknowledgements

Many thanks to all the members of my laboratory, attendings, and endocrine, oncology, and surgery fellows for their long hours, dedication, and passion for helping those who suffer.

To many outside NIH co-investigators

“Patients are our passion and we are their hope”
Pediatric PHEO: Important facts

- 5-10% of all PHEOs
- Peak at age 10 to 13 with male predominance
- Up to 60% (adults: 30%) familial; 45% (20%) extra-adrenal, 50% (10%) multiple or bilateral (adrenal)
- Commonly metastatic if due to SDHB mutations; VHL mutations represent the 2nd most common cause

Neumann et al. NEJM 2002; 346:1459
Benn et al. JCEM 2006; 91:827
Brouwers et al. JCEM 2006; 91:4505