Pheochromocytoma: Diagnostic Evaluation

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Relevant Financial Relationship(s)
None

Off Label Usage
None

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• I am a member of the Endocrine Exam Committee (July 2013 – present)

• As is true for any ABIM candidate who has taken the certification exam, I have signed a Pledge of Honesty in which I have agreed to keep the ABIM exam confidential

• No exam questions will be disclosed in my presentation
Pheochromocytoma—Background

- Catecholamine-secreting tumor usually localized to the adrenal gland
- Frequently sought and rarely found
- When correctly diagnosed and properly treated, it is curable
- When undiagnosed or improperly treated, it can be fatal
Clinical Presentation

- **Prevalence** -- 0.01% to 0.1%
- **Occurrence** -- equally in men and women, primarily in the 3rd through 5th decades
- **Symptoms** -- present in 50% of patients & paroxysmal
Pheo: When to Suspect:

- Hyperadrenergic spells (eg, episodes of forceful palpitations, diaphoresis, headache, tremor, pallor)
  HOWEVER, most patients with spells do NOT have pheo!
- Resistant hypertension
- A familial syndrome that predisposes to pheo/PGL (eg, MEN 2, NF1, VHL, SDHx)
- A family history of pheochromocytoma
- An incidentally discovered adrenal mass (60% of our pheo patients at Mayo Clinic!)
- Pressor response to anesthesia, surgery, or angio
- Onset of hypertension at a young age (eg, <30 yrs)
- Idiopathic dilated cardiomyopathy
Case Detection

Laboratory Evaluation (1):

- Fractionated cats (dopamine, norepinephrine, and epinephrine) & fractionated mets (metanephrine and normetanephrine) by HPLC or tandem mass spectrometry

- At Mayo Clinic, the most reliable case-detection strategy is measuring fractionated mets and cats in a 24-hr urine collection. If clinical suspicion is high, then plasma fx mets are also measured
Case Detection

Laboratory Evaluation (2):

- Although it is preferred that patients not receive any meds during lab testing, Rx with most meds may be continued (all BP-related meds are OK!!!)

- Tricyclic antidepressants (TCAs) interfere most frequently with the interpretation of 24-hr urinary fx cats & mets (TIP: cyclobenzaprine [Flexeril®] is a TCA)

- Rx with TCAs & antipsychotic agents should be tapered & D/C at least 2 wks before testing

- It is also important to recognize that catecholamine secretion may be appropriately ↑ed in situations of physical stress or illness (eg, stroke, MI, CHF, OSA)
Medications That May ↑ Measured Levels of Catecholamines & Metanephrines

- Tricyclic antidepressants
- Levodopa
- Drugs containing adrenergic receptor agonists (e.g., decongestants)
- Amphetamines
- Buspirone and most psychoactive agents (except NOT selective serotonin reuptake inhibitors [SSRIs]; SNRIs may cause <2-fold increases above upper limit of reference range)
- Prochlorperazine
- Reserpine
- Withdrawal from clonidine and other drugs (eg, illicit drugs)
- Ethanol
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Common Sense Tips on Diagnosis

- Suppression testing with clonidine or provocative testing with glucagon, histamine, or metoclopramide are NEVER needed.

- In a pt with **spells**, the degree of ↑ of fx mets & cats should be markedly abnormal—in other words, if a pheo is responsible for “classic pheochromocytoma spells”, then the biochemical tests are **ALWAYS** unequivocally abnormal (eg, >5-fold increases above the upper limit of normal).

- Just because a patient is being treated with a β-adrenergic inhibitor without problems does **NOT** mean they **cannot** have a pheo.
Common Sense Tips on Diagnosis

• Suppression testing with clonidine or provocative testing with glucagon, histamine, or metoclopramide are NEVER needed

• & cats should be markedly abnormal— in other pheochromocytoma spells”, then the biochemical tests are ALWAYS unequivocally abnormal (eg, >5-fold increases above the upper limit of normal)

• Just because a patient is being treated with a \( \beta \)-adrenergic inhibitor without problems does NOT mean they cannot have a pheo
Common Sense Tips on Diagnosis

Additional tips:

✔ ALL biochemical tests may be nl in an asx pheo pt with an adrenal incidentaloma that is discovered in its “pre-biochemical phase”—the good news here is that the imaging phenotype will guide your management.

✔ Imaging phenotype “over rules” biochemical testing any day

Common Sense Tips on Diagnosis

Additional tips:

✓ ALL biochemical tests may be nl in an asx pheo pt with an adrenal incidentaloma that is discovered in its "pre-biochemical phase"—the good news here is that the imaging phenotype will guide your management.

✓ Imaging phenotype "over rules" biochemical testing any day

“Imaging Phenotype”

Radiodensity measured in Hounsfield Units (HU)

-20 HU

+60 HU

More lipid

Benign

Fast contrast washout

>50% at 10 min

Lipid-poor adenoma

ACC

Met

Pheo

Slow contrast washout

<50% at 10 min

Lipid-poor adenoma
Adenoma Imaging Phenotype:

- Hypodense
- Homogeneous
- Precontrast radiodensity < 10 HU
- >50% contrast washout at 10 min
One Exception to “Low Density Rule”:

- The adrenal cyst

Beware of the adrenal “cyst”!
In the clinical setting of an incidentally discovered adrenal mass, pheo is an image-directed diagnosis. In the adrenal incidentaloma patient, the imaging phenotype should "over-rule" biochemistry.
Jan-1999

Jan-2000

Feb-2001

April-2002
Common Sense Tips on Diagnosis

Additional tips:

- Plasma **normetanephrine** has a 15% false positive rate—combine that piece of information with the rarity of pheochromocytoma and you will find that 97% of patients with increased plasma **normetanephrine** will **NOT** have a pheochromocytoma!
81 yr F – ↑BP; CT for RT abd pain
Enhancing mass mid LT kidney consistent with RCCa
Also 1.9 cm LT adrenal mass

CT: HU <10; >50% contrast washout at 10 min
Plasma fx mets:
  normet = 2.23 nmol/L (N < 0.9)
  met = 0.2 (N < 0.5)
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CT: HU <10; >50% contrast washout at 10 min
Plasma fx mets:
normet = 2.23 nmol/L (N < 0.9)
met = 0.2 (N < 0.5)

24-hr urine:
nmet = 595 mcg (N <900)
met = 106 mcg (N < 400)
cats = normal
Plasma Normetanephrine, pg/mL

Non-pheochromocytoma patients

$r=0.270$

$P<0.001$

23% false + > age 60

Sawka et al. *J Clin Endocrinol Metab* 2003 Feb; 88:553-8
Common Sense Tips on Diagnosis

Additional tips:

- Most reference labs in the USA have standardized their 24-hr fx mets & cats assays on nl laboratory volunteers that are drug-free & have nl BP—I have NEVER tested such a patient for pheo!

- Appropriate 24-hr urine cutoffs based on pts tested for pheo, but proved to not have this rare tumor are:
  - Met <400 mcg; Normet <900 mcg; Total met <1000 mcg
  - NE <170 mcg; EPI <35 mcg; DA <700 mcg

- Pts with lab values > these cutoffs either have pheo, severely ill (eg, intensive care unit), or are taking a drug that is causing false positive testing
Diagnosis and Localization of Pheochromocytoma and Paraganglioma

Symptomatic
(eg, resistant hypertension or paroxysms of hypertension, palpitations, perspiration, and headaches)

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Incidentally Discovered Adrenal or Retroperitoneal Mass

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Familial Syndrome that Predisposes to Pheochromocytoma or Paraganglioma

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Lipid rich (eg, pre-contrast CT attenuation ≤10 HU): biochemical testing not needed

Pre-contrast CT attenuation >10 HU)

Plasma fractionated metanephrines or 24-hr urine fractionated metanephrines and catecholamines

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Normal

Normal

Normal

Normal

Abnormal

Abnormal

Abnormal

Abnormal

Exclude interfering drugs & consider cross sectional computed imaging of abdomen & pelvis

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Caution: small (eg, <1.5 cm) tumors may not be biochemically detectable

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Exclude interfering drugs & consider additional imaging to confirm tumor & exclude additional tumors

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Annual biochemical testing

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Plasma fractionated metanephrines or 24-hr urine fractionated metanephrines and catecholamines

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Localization (1)

- We **usually** do not proceed with localization studies until biochemical studies have confirmed the dx of a catecholamine-secreting tumor.
- Computer-assisted imaging of the adrenal glands abdomen with contrast-enhanced CT should be the first localization test (sensitivity, >95%; specificity, >65%).
- Approximately 85% of these tumors are found in the adrenal glands, and 95% are found in the abdomen and pelvis.
Average size = 4.5 cm
Some are smaller
Some are bigger
Localization (2)

- \(^{123}\)I-Metaiodobenzylguanidine (MIBG) scintigraphy is indicated if abdominal imaging is negative

- \(^{123}\)I-MIBG is superior to \(^{131}\)I-MIBG because the photon energy allows single photon emission computed tomographic (SPECT) images

- If a typical (<10 cm) unilateral adrenal pheo is found on CT or MRI, \(^{123}\)I-MIBG scintigraphy is superfluous and may even confuse the clinician

- If the adrenal pheo is >10-cm in diameter or if a PGL is found, then \(^{123}\)I-MIBG scintigraphy or 68-Ga-DOTATATE PET is indicated because the pt has increased risk of malignant disease & additional PGLs
68-yr-old F with labile hypertension
Markedly increased 24-hr urine NE and normet
$^{123}\text{I-MIBG Scan}$
Retro-cardiac PGL
RT abdominal PGL

- Tumor
- Uncinate of pancreas
- Duodenum
- SMV
LT abdominal PGL

Tumor

Left common phrenic vein

Left Renal vein

Left ovarian vein

+SDHB c.649C>T (p.R217C)
Special Comments on MIBG

- $^{123}$I-MIBG is taken up in normal adrenal glands & it is usually asymmetric. Inexperienced radiologists will typically call the LT adrenal suspicious on $^{123}$I-MIBG scintigraphy because it is much more easily seen.

- Never remove an adrenal gland based on $^{123}$I-MIBG without CT/MRI corroboration. Again, a symptomatic pheo typically >4.5 cm in diameter.
“MIBG Traps”

44-yr-old man
New onset ↑BP & spells

24-hr urine:
  nmet = 687 mcg
  met = 143 mcg

123-I-MIBG: “+ LT”

CT: “+ LT adrenal”

Lap LT adx: normal cortex & medulla
“MIBG Traps”

44-yr-old man
New onset ↑BP & spells

24-hr urine:
- nmet = 687 mcg
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123-I-MIBG: “+ LT”
CT: “+ LT adrenal”

Lap LT adx: normal cortex & medulla

MIBG Pearls:
There is a normal asymmetry in adrenal uptake
LT > RT

Sx pheo must have a sizable factory (eg, > 3 cm)
Localization (3)

- It is important to recognize the meds that may interfere with $^{123}$I-MIBG uptake (eg, tricyclic antidepressants, labetalol, CCBs) because they should be D/C before imaging.

- Localizing procedures that also can be used, but are rarely required, include computer-assisted imaging of the chest, neck, and head.

- Other localizing studies, such as somatostatin receptor imaging with $^{111}$In-DTPA-pentetreotide, may also be considered; but the sensitivity of somatostatin receptor imaging with $^{111}$In-DTPA-pentetreotide is low.
Localization (4)

- Although positron emission tomography (PET) scanning with $^{18}$F-fluorodeoxyglucose (FDG) or $^{11}$C-hydroxyephedrine or 6-$^{[18}$F$]$fluorodopamine or $^{68}$Ga-DOTATATE PET-CT can identify PGLs, these expensive techniques probably should be reserved for identifying sites of metastatic disease and in patients with negative $^{123}$I-MIBG scintigraphy.
FDG-PET to determine extent of disease

50 yr F  
*SDHB* R230L  
24-yr course

54 yr F  
Mutation neg  
37-yr course

42 yr M  
*SDHD* deletion  
17-yr course
Serial FDG-PET to monitor tumor progression

December, 2004
August 2005
May 2006

47-yr F SDHB R90X
FDG-PET to monitor efficacy of therapy

CVD x 8 mo

March, 2006

January, 2007
61-yr-old woman: 2010 – 3 cm LT adrenal pheo resected; 2013 – polyostotic metastatic disease detected

In Nov 2017: 123-I-MIBG 68-Ga DOTATATE PET-CT
Localization (4)

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- Selective venous sampling for catecholamines is usually misleading and should be avoided.
Adrenal Venous Sampling for Catecholamines: A Normal Value Study

E. Marie Freel, Anthony W. Stanson, Geoffrey B. Thompson, Clive S. Grant, David R. Farley, Melanie L. Richards, and William F. Young, Jr.

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Context: Pheochromocytomas are rare, but potentially fatal, neoplasms. The diagnosis and localization of pheochromocytoma can be challenging, and recently there has been some debate regarding the role for adrenal venous sampling (AVS). The utility of AVS in this setting is hampered by a lack of normative value data for adrenal vein catecholamine concentrations and the reliability of lateralization ratios. We sought to address these concerns by analyzing AVS catecholamine concentrations from patients who did not have pheochromocytoma.

Design/Setting: Eighteen patients underwent successful AVS for evaluation of cortisol-producing adrenal masses. All had normal 24-h urinary excretion of fractionated catecholamines and metanephrines.
18 non-pheo pts: RT AV-to-LT AV EPI gradient was as high as 83:1 (median, 2.1:1; \( P < .02 \)) Although less striking, similar findings were also seen for NE.
Freel EM et al.  
*JCEM*, 2010 95:1328-32
NEVER do AVS for pheo!
Common Sense Tips on Localization

- The tumor can always be found in the sx pt with pheo—the avg diameter is 4.5 cm. **If you are having trouble localizing a pheo, it is usually because your pt does not have a pheo & you have ignored some of the biochemical dx tips**

- MRI is over-rated

- EPI/metanephrine-predominant tumors will always be localized to the adrenal medulla or Organ of Zuckerkandl

- NE/normetanephrine-predominant tumors may arise from the adrenal medulla or from sympathetic paraganglioma in the abd, pelvis, chest, or neck
Treatment (1)

☑ Combined $\alpha$- and $\beta$-adrenergic blockade is one approach to control BP & prevent intraop hypertensive crises

☑ We start $\alpha$-adrenergic blockade with phenoxybenzamine 7 to 10 days preop to normalize BP & expand contracted blood volume

☑ BP should be monitored 2x/d. Target BP is $<120/80$ mm Hg (seated), with SBP $>90$ mm Hg (standing); both targets should be modified on basis of the patient’s age and comorbid disease

Treatment (2)

- On the second or third day of \( \alpha \)-adrenergic blockade, pts are encouraged to start a diet high in sodium content (\( \geq 5,000 \) mg daily)
- This degree of volume expansion may be contraindicated in patients with CHF or renal insufficiency
- After adequate \( \alpha \)-adrenergic blockade has been achieved, \( \beta \)-adrenergic blockade is initiated, which typically occurs 2 to 3 days preoperatively
- The last oral doses of \( \alpha \)- & \( \beta \)-adrenergic blockers are given early in the morning on the day of surg
Long-Term Postop F/U

- 1 to 2 wks postop we measure fx cats & mets in a 24-h urine or plasma fx mets

- If levels are normal, the resection of the pheo should be considered complete

- Increased levels of cats & mets detected postop are consistent with residual tumor due to either a 2nd primary lesion or occult metastases
Long-Term Postop F/U

- 24-h urine fx cats & mets or plasma fx mets should be checked annually for life
- Annual biochemical testing assesses for metastatic disease, tumor recurrence in the adrenal bed, or delayed appearance of multiple primary tumors
- Follow-up CT or MRI are not needed unless the mets/cats become elevated or if a) the original tumor was associated with minimal catecholamine excess b) the patient has a $SDHx$ mutation
Genetic Causes

Hypoxic Pathway – “Cluster 1” (NE/Normeta):
- **SDHx**: SDHA, SDHAF2, SDHB, SDHC, SDHD
- **VHL**
- **FH**
- **HIF2α**
- **EGLN1 (PHD2), EGLN2 (PDH1)**
- **KIF1B**
- **IDH1**
- **MDH2**
- **SLC25A11**
- **DMT3A**

95% of the causative germline mutations are: **SDHx, VHL, RET, NF-1**

Kinase Signaling Pathway – “Cluster 2” (EPI/Meta):
- **RET**
- **NF-1**
- **MAX**
- **TMEM127**
Genetic Testing

- 40% of patients with pheo/PGL have disease-causing germline mutations
- Hereditary pheo/PGL tumors typically present at a younger age than sporadic neoplasms
- Genetic testing should be considered if a patient has one or more of the following:
  1) PGL
  2) bilateral adrenal pheo
  3) unilateral adrenal pheo & + FHx of pheo/PGL
  4) unilateral adrenal pheo & young age (<45 y)
  5) other clinical findings suggestive of one of the syndromic disorders
Endocrine Hypertension.