Endocrine Hypertension: Case-Based Update on Pheochromocytoma and Primary Aldosteronism

William F. Young, Jr., MD, MSc
Professor of Medicine, Mayo Clinic, Rochester, MN USA
Division of ENDOCRINOLOGY, DIABETES, METABOLISM & NUTRITION

Typical Case: 37-Year-Old Man
Hypertension x 14 yrs:
- BP accelerated over the past 1 yr—previously 3 drugs with good control; now 5 drugs (amlodipine 10 mg/d, carvedilol 50 mg bid; losartan-HCTZ 100-25 mg/d; spironolactone 50 mg/d)
- 6 mo ago hypokalemia found: K⁺ = 3.0 mEq/L
- BP improved with addition of SPL 4 mo ago
- Physical exam: normal phenotype, BP = 148/92 mm Hg, HR 70 bpm, BMI 52 kg/m²
- Initial labs: Na⁺ = 139 mEq/L, K⁺ = 4.4 mEq/L, creatinine = 1.1 mg/dL

Which patient has the pheo?
A. Hypertension
   Plasma normetanephrine increased 40% above ULN
B. Normal BP
   Normal plasma fractionated metanephrines

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

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Arizona-AACE 2018 Annual Meeting, Sep 8th, 10:15-11:15 AM
DISCLOSURE*

Relevant Financial Relationship(s): 
None

Off Label Usage: 
None

*A provider must disclose the above information to learners prior to beginning of the educational activity (ACCME)
Disclosure of ABIM Service

• 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
Primary Aldosteronism (PA)

Why is PA important for the clinician?

1. PA is the most common cause of secondary hypertension: \( \approx 5\% \) of all people with high blood pressure

2. The diagnosis of PA provides the clinician with a unique opportunity—to either cure hypertension or to use targeted pharmacotherapy and prevent end stage PA: renal failure and cardiac disease

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OK, so who should be tested for PA?
1.0 Case detection

1.1 We recommend case detection of primary aldosteronism (PA) in patients with sustained blood pressure (BP) above 150/100 mm Hg on each of three measurements obtained on different days, with hypertension (BP >140/90 mm Hg) resistant to three conventional antihypertensive drugs (including a diuretic), or controlled BP (<140/90 mm Hg) on four or more antihypertensive drugs; hypertension and spontaneous or diuretic-induced hypokalemia; hypertension and adrenal incidentaloma; hypertension and sleep apnea; hypertension and a family history of early onset hypertension or cerebrovascular accident at a young age (<40 years); and all hypertensive first-degree relatives of patients with PA. (1|+++∞)}
But, clinicians are not testing for PA. Having worked in this field for more than 3 decades, it is frustrating to see patients who were never tested for PA when they were first diagnosed with hypertension, but rather only after they have developed irreversible stage 4 to 5 chronic kidney disease. Clinical practice guidelines have not been effective in driving more clinicians to consider case detection testing for PA. Could the guidelines be too complicated with rules on medications and by focusing on recommending subsets of patients to be tested for PA?
When to Consider Testing for Primary Aldosteronism:
• All patients with hypertension should be tested at least once

Case Detection Test:
Morning blood sample in seated ambulant patient
• Plasma aldosterone concentration (PAC)
• Plasma renin activity (PRA) or plasma renin concentration (PRC)

Confirmatory Testing (if spontaneous ↓K⁺ absent):
• 24-h urine for aldosterone and sodium on a high sodium diet

PAC ≥10 ng/dL (≥277 pmol/L)
and
↓ PRA (<1.0 ng/mL/hr) or ↓ PRC (< lower limit of detection)
When to Consider Testing for Primary Aldosteronism:
- All patients with hypertension should be tested at least once

PAC $\geq 10$ ng/dL ($\geq 277$ pmol/L) and
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Case Detection Test:
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**NOTE:** only 30% of patients with PA are hypokalemic—there is no clinical phenotype!

**NOTE:** patients can be on any sodium diet and any BP meds INCLUDING SPL and EPL*

**NOTE:** 90% of patients with APA have a PAC $\geq 15$ ng/dL ($\geq 416$ pmol/L)
Caveat on SPL and EPL

There are potentially clinically important issues with the following drugs:

- **Mineralocorticoid receptor antagonists** – It may be difficult to interpret data obtained from patients treated with a mineralocorticoid receptor antagonist (spironolactone and eplerenone). These drugs prevent aldosterone from activating the receptor, resulting sequentially in sodium loss, a decrease in plasma volume, and an elevation in PRA, which will reduce the utility of the PAC/PRA ratio. For this reason, spironolactone and eplerenone should not be initiated until the evaluation is completed and the final decisions about treatment are made.

However, there are exceptions to this rule. For example, if the patient is hypokalemic despite treatment with spironolactone or eplerenone, then the mineralocorticoid receptors are not fully blocked and PRA or PRC should be suppressed in such a patient with primary aldosteronism. In addition, most patients with primary aldosteronism who are treated with mineralocorticoid receptor antagonists are given subtherapeutic doses. Thus, PAC and PRA should be measured in patients treated with spironolactone or eplerenone, and if PRA is suppressed, these medications are not interfering. Thus, if PRA is suppressed, case-detection testing, confirmatory testing, and adrenal vein sampling (AVS) can be performed without discontinuing the mineralocorticoid receptor antagonists. However, if PRA is not suppressed, then the mineralocorticoid receptor antagonist should be discontinued for four to six weeks before retesting. Other potassium-sparing diuretics, such as amiloride and triamterene, usually do not interfere with testing unless the patient is on high doses.

- **ACE inhibitors, ARBs, direct renin inhibitors** – Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and direct renin inhibitors could potentially elevate PRC and have variable effects on PRA in patients with primary aldosteronism. Thus, in a patient treated with one of these drugs, a PRA >1 ng/mL/hour does not exclude the diagnosis of primary aldosteronism. On the other hand, a strong predictor for primary aldosteronism is a PRA <1 ng/mL/hour or low PRC in a patient taking one of these drugs.

*UpToDate: “Diagnosis of primary aldosteronism”
**Caveat on SPL and EPL**

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So, this is simply understanding physiology. If PRA is suppressed in a patient taking SPL or EPL (or any medication), you can do case detection testing, confirmatory testing, and even AVS!

*UpToDate: “Diagnosis of primary aldosteronism” WF Young. Accessed August 1, 2018.*
Confirmatory Testing:

- Not needed if spontaneous hypokalemia, PAC >20 ng/dL (>555 pmol/L), and PRA <1 ng/mL/hr*

- Saline suppression test, captopril stimulation test, fludrocortisone suppression test, or **oral sodium loading test**
  - In the patient with undetectable PRA, and when the 24-hr urinary Na⁺ is >200 mEq, a 24-hr urinary aldosterone of >12 µg (>33 nmol/d) confirms PA

Subtype Testing:

✓ Unilateral adrenalectomy (adx) in pts with aldosterone-producing adenoma (APA) results in normalization of $\downarrow K^+$ in all; hypertension is improved in all & cured in $\approx 30\%$ to $40\%$*

✓ In bilateral idiopathic hyperaldosteronism (IHA), unilateral adx does not cure PA. Bilateral adx is not a “good trade.” Patients with IHA should usually be treated medically

✓ .:. for those pts that want to pursue a surgical cure, the accurate distinction between the subtypes of PA is a critical step

Subtype Testing:
✓ We start with adrenal-dedicated abdominal CT
✓ When a solitary, hypodense, & unilateral macroadenoma (> 1 cm & < 2 cm) & nl contralateral adrenal morphology are found on CT in a young pt (< 35 yrs) with severe PA (eg, PAC ≥30 ng/dL [≥832 pmol/L] and spontaneous hypokalemia), unilateral lap adx is a reasonable Rx option*

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- However, 95% of patients are >35 yrs old or have non-localizing CT scans—in these cases, if the patient wants to pursue the surgery, additional testing is needed.
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Hypertension x 14 yrs:

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☑ 6 mo ago hypokalemia found: $K^+ = 3.0\; \text{mEq/L}$

☑ BP improved with addition of SPL 4 mo ago

☑ Physical exam: normal phenotype, BP = 146/92 mm Hg, HR 70 bpm, BMI 52 kg/m$^2$

☑ Initial labs: $Na^+ = 139\; \text{mEq/L}$, $K^+ = 4.4\; \text{mEq/L}$, creatinine = 1.1 mg/dL
PAC/PRA Ratio
- PAC = 33 ng/dL (915 pmol/L)
- PRA = <0.9 ng/mL/hr

To be honest, I don’t look at a “ratio.” The reference range for ratios are impacted in a major way by the denominator.

For example, a PAC of 3 ng/dL and a PRA of 0.1 ng/mL/hr has a ARR of 30. This is NOT PA!

If PAC is around 15 ng/dL (>8 ng/dL or >10 ng/dL or >12 ng/dL – just use something!) and if PRA is low (eg, <1 ng/mL/hr), this is a + case detection test.
PAC/PRA Ratio
- PAC = 33 ng/dL (915 pmol/L)
- PRA = <0.9 ng/mL/hr

But, wait, what about:
ARB?
HCTZ?
β-Blocker?
MR antagonist

I NEVER stop BP meds (including SPL & EPL) for case detection testing
Nothing causes false + testing IF you use a PAC cut-off—use 10 or 12 or 15 ng/dL – just use something!
Now, does he have APA or IHA?

Does it matter?

Ask the patient . . .

He would like to pursue the surgical option to cure primary aldosteronism with the knowledge that he likely has concomitant essential hypertension which will not be cured by an operation. However, if he does have unilateral adrenal disease, surgery will cure the aldosterone excess, make his blood pressure markedly better, and resolve the hypokalemia. With that understanding, he would like to
Adrenal CT: Radiologist report: “normal adrenals”

He wants a surgical cure for his PA to resolve hypokalemia and improve BP. Now what?
## Adrenal Venous Sampling

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<tr>
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<tr>
<td>Aldosterone(S)</td>
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# Adrenal Vein Sampling*

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<th>Vein</th>
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<th>Cortisol (C) mcg/dL</th>
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<th>Aldosterone Ratio</th>
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<td>IVC</td>
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<td>20</td>
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</table>

*Cosyntropin infusion 50 mcg/hr
The patient I am presenting

A. Received fresh labeled "left adrenal gland" is a 13.35 gram, 4.1 x 3.2 x 1.1 cm adrenal gland, with a 1.1 x 1.1 x 0.7 cm yellow-brown soft mass located in the cortex, which does not extend beyond the adrenal gland. Photo taken. Representative sections are submitted. Grossed by VVS.
A. Received fresh labeled "left adrenal gland" is a 13.35 gram, 4.1 x 3.2 x 1.1 cm adrenal gland, with a small yellow-brown soft mass located in the cortex, which does not extend beyond the adrenal gland. Photo taken. Representative sections are submitted. Grossed by VVS.

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<td>&lt;4.0</td>
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Postop Care:

- Check serum K$^+$ once weekly x 4
- 5% of patients develop clinically important hyperkalemia (K$^+>5.2$ mEq/L); correlates with degree of contralateral adrenal suppression during AVS*
- If serum K$^+$ rises above 5.2 mEq/L, Rx with fludrocortisone 0.1 mg/d; monitor K$^+$ weekly and cut fludrocortisone in half if serum K$^+ <4.5$ mEq/L, and so on. Typical duration of fludrocortisone Rx is 2 wks (some take longer)

Follow-up: 3 Months

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CHIEF COMPLAINT/PURPOSE OF VISIT
Telephone call.

IMPRESSION/REPORT/PLAN

#1 Primary aldosteronism—LEFT adrenal aldosterone—status post laparoscopic left adrenalectomy September 28, 2017

I talked with Mr. [redacted] over the telephone today. He recovered well from his laparoscopic adrenal surgery. His weekly potassium checks for four weeks were all in the mid to high 4s. His blood pressure has been dropping. Today his blood pressure is 118/72 mm Hg. He remains on amlodipine 10 mg daily, carvedilol 50 mg twice daily, and hydrochlorothiazide 12.5 mg daily.
Role for adrenal venous sampling in primary aldosteronism

William X Yang, MD, Anthony M. Sommers, MD, Geoffrey S. Thompson, MD, Chris S. Grant, MD, Jane C. Kerley, MD, and Jan A. van Heerden, MD, Chil, Houston, Texas

Background. The aim of this study was to determine the effect of adrenal venous sampling (AVS) in the management of patients with primary aldosteronism.

Methods. From September 1999 through October 2003, 203 patients with primary aldosteronism (mean age, 53 years; range, 12-80; 113 men) were evaluated prospectively for AVS on the basis of degree of aldosterone excess, age, fasting for surgical treatment, and ambulatory monitoring (24-hr) findings. Results. Baseline data were completed in 199 patients (97.6%). Among the 110 patients (54.7%) with unilateral aldosterone hypersecretion, 24 (21.8%) of 55 patients with normal adrenal CT findings, 31 (31.1%) of 31 with unilateral norepinephrine (N.E.) values at or above 0.2 ng/mL, and 7 (36.8%) of 19 with bilateral norepinephrine were identified. Among the 89 patients (44.9%) with normal CT, 38 (42.6%) of 90 patients with unilateral norepinephrine >0.2 ng/mL, and 3 (15.4%) of 20 with bilateral norepinephrine were identified. Conclusion. On the basis of CT findings alone, 13 patients (12.7%) would have been incorrectly classified as aldosteronomas, and 19 (18.2%) might have had unnecessary imaging studies. AVS is an essential diagnostic test in distinguishing between unilateral and bilateral aldosterone hypersecretion. (Surg Today 2007;37:120-25.)

Univ of Michigan – 2017

Discordance between imaging and immunohistochemistry in unilateral primary aldosteronism

Aya T. Nakaib 1 | Kazutaka Nakaib 1 | James B. Byrd 1 | James J. Shields 1

Thomas J. Giordano 1 | Barbara S. Miller 1 | William E. Rainey 1,2 | Richard J. Anfinsen 3,4 | Adina F. Teer 1

Background: Aldosterone-producing adenoma (APA) is a histologically solitary adrenal tumor that is responsible for the majority of cases of primary aldosteronism (PA). Objective: To determine the discordance between imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) and immunohistochemistry (IHC) in APA.

Methods: From January 2007 to January 2016, patients with unilateral PA were identified from a tertiary referral center. Unilateral PA was defined as aldosterone production in an adrenal gland from a single adrenal mass. Patients were excluded if they had undergone a surgical resection for PA before study inclusion. Patients with at least one histologically confirmed APA were included. Results: In total, 17 patients with unilateral PA were included. Of these, 14 patients had at least one IHC result. In 12 of 14 patients, discordance was found between CT and IHC results, with 9 APA patients being incorrectly classified as having a normal adrenal gland based on CT imaging. ALDO stain was positive in all 12 patients with discordant results (11/12 different IHC results). Conclusion: Imaging results may not accurately reflect the presence of an APA. These results highlight the importance of IHC in confirming the histopathological diagnosis of PA.
Accuracy of CT = 56% (Consistent with >80 other studies in the literature)

Based on CT:
- 46 patients (24%) would have been bypassed for curative surgery
- 42 pts (22%) would have had noncurative surgery

Based on CT:
- 19 patients (12%) would have been bypassed for curative surgery
- 48 pts (30%) would have had noncurative surgery
Selective: Eplerenone
Nonselective: Spironolactone

If severe PA and markedly asymmetric on AVS, consider unilateral surgical debulking.

Mineralocorticoid-Receptor Antagonist

Laparoscopic Adrenalectomy

If needed for BP control, add diuretic, CCB, and/or ACE-I/ARB

NOTE: correct dose of SPL (qd) or EPL (bid) is whatever it takes for a high-nl serum K⁺ without the aid of KCl supps.
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
Pheo: Clinical Presentation

- **Prevalence** -- 0.01% to 0.1%
- **Occurrence** -- equally in men and women, primarily in the 3rd through 5th decades
- **Symptoms** -- in 2018 symptoms are present <50% of patients; when present, typically paroxysmal
- **Mode of Diagnosis** -- has changed dramatically over the past 90 years*

*Gruber et al. *submitted* 2018
Mode of Diagnosis of PPGL at Mayo Clinic*

*Gruber et al. submitted 2018

- Paroxysms or hypertension
- Incidentally discovered
- Abdominal mass
- Familial/genetic testing

<table>
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<tr>
<th>Period</th>
<th>Paroxysms or Hypertension</th>
<th>Incidentally Discovered</th>
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<td>61</td>
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<td>27</td>
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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 (61% of our pheo patients at Mayo Clinic!)
- Pressor response to anesthesia, surgery, angiography, dexamethasone, β-blocker
- Onset of hypertension at a young age (eg, <30 yrs)
- Idiopathic dilated cardiomyopathy
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 (61% of our pheo patients at Mayo Clinic!)
- Pressor response to anesthesia, surgery, angiography, dexamethasone, β-blocker
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NOTE: 3-5% of all adrenal incidentaloma patients have pheo
Pheo: Case Detection

- 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 (if possible) at least 2 wks (4 wks best) 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 (including cyclobenzaprine [Flexeril®])
- 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 (e.g., illicit drugs)
- Ethanol
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NOTE: With current assay methodology, antihypertensive meds DO NOT interfere with testing!
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 above the ULN)
Which patient has the pheo?

A. Hypertension
   Plasma normetanephrine increased 40% above ULN

B. Normal BP
   Normal plasma fractionated metanephrines
Which patient has the pheo?

A. Hypertension
   Plasma normetanephrine increased 40% above ULN

B. Normal BP
   Normal plasma fractionated metanephrines

NOTE: In the adrenal incidentaloma patient, the imaging phenotype overrules biochemical testing! . . . and 97% of patients with mild ↑ in plasma normetanephrine do NOT have 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 normal in a patient 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

NOTE: thinking that a vascular adrenal mass cannot be a pheochromocytoma because of normal biochemistry is a “common” mistake!

Pheo Imaging Phenotype:

- Dense and vascular
- Inhomogeneous with cystic degenerative areas
- Precontrast radiodensity >20 HU
- <50% contrast washout at 10 min
Adenoma Imaging

Phenotype:

- Hypodense
- Homogeneous
- Precontrast radiodensity <10 HU
- >50% contrast washout at 10 min
Additional tips:

- Fractionated 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!*

- However, when plasma metanephrine is even mildly elevated take it seriously!

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

✓ 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

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NOTE: If patient is already on a \( \beta \)-B, don’t stop it, simply add your \( \alpha \)-blocker

NOTE: Except for CCBs and \( \beta \)-Bs, stop other BP meds so that you can get on max doses of your \( \alpha \)-blocker

NOTE: If you patient has normal BP, still \( \alpha \)-block—target low normal SBP for age and maximize dietary sodium

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 morning of surgery
Treatment (2)

- On the second or third day of α-adrenergic blockade, pts are encouraged to start a diet high in sodium content (≥5,000 mg daily).
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- After adequate α-adrenergic blockade has been achieved, β-adrenergic blockade is initiated, which typically occurs 2 to 3 days preoperatively.
- The last oral doses of α & β-adrenergic blockers are given morning of surgery.

- We block asymptomatic, normotensive patients too.
- If HR is <80 bpm and BP controlled, you may not need a β-blocker.
- We have been using more doxazosin because of the ↑ cost of phenoxybenzamine—in that setting we add a CCB to the doxazosin.
Postop F/U (1)

- 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
- ↑ed 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 (2)

- 24-h urine fx cats & mets or plasma fx mets should be checked annually for **life** (metastatic disease can be detected as late as **50 yrs** after the operation*)

- 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 PPGL germline mutation

Genetic Causes

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

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

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

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

2018 Take Home Points:

• **Primary aldosteronism:**
  - It is common; most have normal serum K⁺
  - Test for it!! – Morning PAC & PRA – all pts with ↑BP
  - Don’t worry about BP meds (eg, ARB, ACE-I, diuretics, MRAs)
  - Don’t trust CT
  - If you plan to send patients to surgery, find or develop a good AVS program

• **Pheochromocytoma/paraganglioma:**
  - It is rare
  - Most positive case detection tests are false-positive nor metanephrine—know the drugs that interfere
  - Incidental adrenal mass → rely on imaging phenotype
  - MRI is over rated
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