Endocrine Hypertension

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Disclosure

Michael McDermott has no conflict of interest or relationships to disclose in relation to this educational activity.

Learning Objectives

- **Explain the evaluation and management of primary aldosteronism.**
- **Discuss the evaluation and management of pheochromocytomas and paragangliomas.**
- **Review the clinical features and evaluation of Cushing's syndrome and Acromegaly.**

Case

A 31 year old man has hypertension which remains elevated on 3 antihypertensive medications. No family history of hypertension.
Meds: Ramipril 10 mg, Amlodipine 10 mg, Metoprolol XL 50 mg
Exam: BP 158/92 P 68 Ht 6'1" Wt 235 lb.
Physical examination is normal otherwise.
Labs: Na 142 mEq/L, K 3.1 mEq/L, Creatinine 0.9 mg/dl

You decide to evaluate for causes of secondary hypertension.

What initial evaluation would have the highest yield?
1. Plasma metanephrines
2. Plasma aldosterone and plasma renin activity
3. 24 hour urine cortisol excretion
4. Renal artery doppler ultrasound

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Labs: Na 142 mEq/L, K 3.1 mEq/L, Creatinine 0.9 mg/dl
Plasma Aldosterone 38 ng/dl (normal: 1-21)
Plasma Renin Activity < 0.6 ng/ml/hr (normal: 0.6-4.3)

What is your interpretation of these results?
1. Diagnostic of primary aldosteronism
2. Possible false positive due to ACE inhibitor
3. Possible false positive due to calcium channel blocker
4. Possible false positive due to beta blocker

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What do you recommend now?
1. Stop current medications. Repeat aldosterone and renin levels
2. Confirmatory testing: measure aldosterone after saline infusion
3. Abdominal CT scan
4. Adrenal vein sampling

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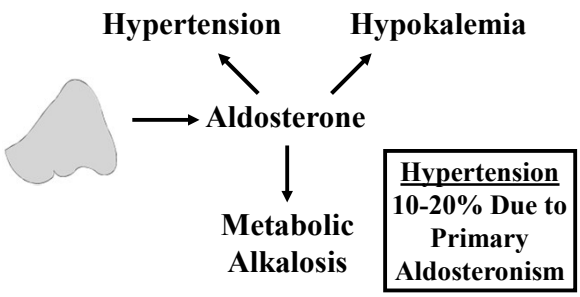
Plasma Aldosterone 38 ng/dl (normal: 1-21)
Plasma Renin Activity < 0.6 ng/ml/hr (normal: 0.6-4.3)
Abdominal CT: 2.6 cm lipid rich left adrenal adenoma

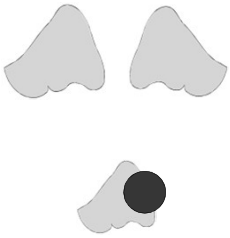
What do you recommend now?
1. Adrenal vein sampling for aldosterone and cortisol
2. CT guided biopsy of left adrenal mass
3. Long-term treatment with an aldosterone receptor antagonist
4. Surgery to remove left adrenal adenoma

Primary Aldosteronism

Primary Aldosteronism
Pathophysiology



Primary Aldosteronism
Main Subtypes



Bilateral Adrenal Hyperplasia (Idiopathic Hyperaldosteronism)

66%

Aldosterone Producing Adenoma (APA)

34%

Primary Aldosteronism
Which Hypertensive People to Screen

- **BP > 150/100 Sustained**
- **BP > 140/90 on 3 BP Drugs**
- **BP controlled on ≥ 4 BP Drugs**
- **Hypokalemia (spontaneous or diuretic induced)**
- **All hypertensive patients –recommend by many**
- **Adrenal incidentaloma**

Young WF. J Intern Med 2019; 285:126-148.
Vaidya A. J Clin Endocrinol Metab 2020; 105:3771-83.
Mehdi A. Cleve Clin J Med 2021; 88(4):221-7.

Primary Aldosteronism
Screening Tests

Random Sample

Plasma Aldosterone (PA)

Plasma Renin Activity (PRA)

Positive Screen

- **PA > 5 ng/dl and PRA < 1 ng/ml/hr**
- **PA/PRA Ratio > 20**

For Direct Renin Assay
PRA = Direct Renin / 8

Primary Aldosteronism

False Positive Tests do not Occur

Significant ↑ Aldosterone and ↓ Renin

Nothing Else Causes This
Positive Results = Positive Results

You Can Test Any Patient Any Time
Without Stopping Medications

Young WF. J Intern Med 2019; 285:126-148.
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Primary Aldosteronism

False Negative Tests – Medications

↓ Aldosterone/Renin Ratio

Medication	Aldosterone	Renin	ARR
ACE Inhibitor	↓	↑↑	↓
AR Blocker	↓	↑↑	↓
Ca Channel Blocker	→↓	↑	↓
K Wasting Diuretic	→↑	↑↑	↓
K Sparing Diuretic	↑	↑↑	↓

Primary Aldosteronism

Medications That Can Be Used During Testing

- **Hydralazine**
- **Prazosin**
- **Doxazosin**
- **Terazosin**
- **Verapamil Slow Release**

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Primary Aldosteronism

False Negative Tests – Other Conditions

↓ Aldosterone/Renin Ratio

Condition	Aldosterone	Renin	ARR
Hypokalemia	↓	→ ↑	↓
Pregnancy	↑	↑↑	↓
Renovascular HTN	↑	↑↑	↓
Malignant HTN	↑	↑↑	↓

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Primary Aldosteronism

Confirmatory Testing

Sodium Loading Tests

Oral Salt Load (High NaCl Diet x 3 Days)

IV Saline Infusion (2 L NS over 4 Hours)

Positive Diagnosis

Oral Salt Load

- **24 hr Urine Aldosterone (3rd day) > 12 ug**

IV Saline Infusion

- **Plasma Aldosterone > 10 ng/dl**

Medication Restrictions:
Spironolactone

Primary Aldosteronism

Confirmatory Testing – When Not Needed

All 3 Present

- **Spontaneous Hypokalemia**
- **Plasma Renin Suppressed**
- **Plasma Aldosterone > 20 ng/dl**

Nothing Else Causes This

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Vaidya A. J Clin Endocrinol Metab 2020; 105:3771-83.
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Primary Aldosteronism

Subtype Classification

Only If Surgery is Being Considered

- **CT Adrenal Glands – All Patients**
- **Adrenal Vein Sampling – Many Patients**

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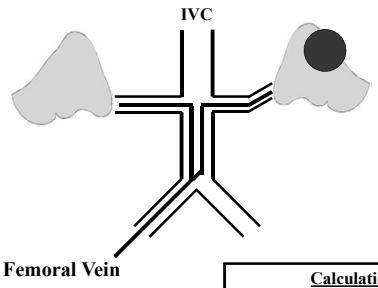
Primary Aldosteronism

Adrenal Vein Sampling



Calculations
Aldosterone Side to Side Gradient
Aldosterone to Cortisol Gradient

Primary Aldosteronism

Adrenal Vein Sampling – When Not Needed?

All 3 Present

- **Age: < 35 Years**
- **Plasma Aldosterone: Markedly Elevated**
- **CT Scan: Unilateral Cortical Adenoma**

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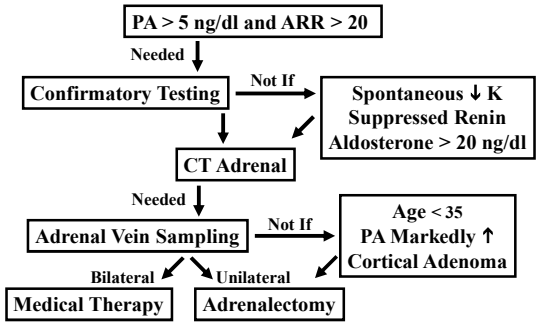
Primary Aldosteronism

Evaluation and Management

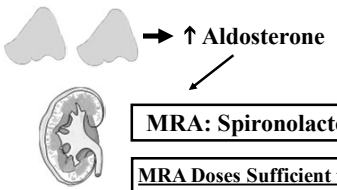


Adapted from: Funder J, J Clin Endocrinol Metab. 2016;101(5):1889-1916

Primary Aldosteronism

Bilateral Adrenal Hyperplasia - Medical Treatment

Mineralocorticoid Receptor Antagonists (MRA) **Plus** **Additional BP Meds as Needed**



↑ Aldosterone

ACE-I
ARB
CCB

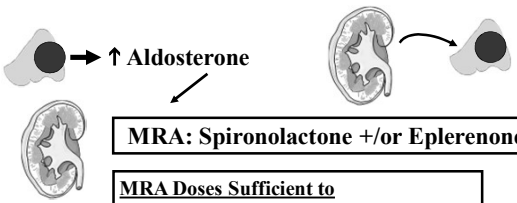
MRA: Spironolactone +/or Eplerenone

MRA Doses Sufficient to
Maintain K in Upper ½ Normal Range
Without K Supplements

Primary Aldosteronism

Aldosterone Producing Adenoma – Surgery (+ Pre-op)

Pre-Operative: MRA **Then** **Adrenalectomy**



↑ Aldosterone

MRA: Spironolactone +/or Eplerenone

MRA Doses Sufficient to
Maintain K in Upper ½ Normal Range
Without K Supplements

Q1

Case

A 21 year old man present with recent onset of hypertension and headaches. He also acknowledges having intermittent palpitations and episodes of profuse sweating. He informs you that his sister had similar symptoms and a rare adrenal tumor was found.
Medications: None
Exam: BP 178/98 P 88 Ht 5'8" Wt 171 lb
Physical examination is normal otherwise.

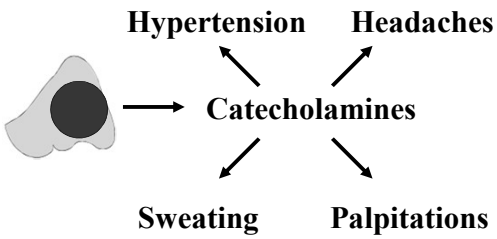
You decide to evaluate for causes of secondary hypertension.

What initial tests would have the highest yield?
1. Plasma metanephrines
2. Plasma aldosterone and plasma renin activity
3. 24 hour urine cortisol excretion
4. Renal artery doppler ultrasound

Pheochromocytoma
Paraganglioma

Pheochromocytoma / Paraganglioma

Pathophysiology



Pheochromocytoma Triad
Headaches, Sweating, Palpitations

Hypertension
0.1-0.01% Due to Pheochromocytoma

Pheochromocytoma / Paraganglioma

General

Prevalence is Low

1/1,000-10,000 of Hypertensive Patients

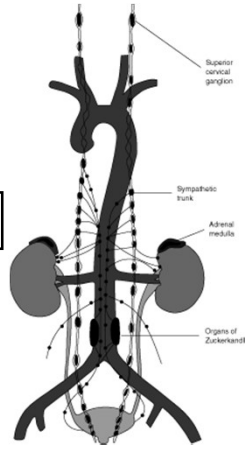
Frequently Sought, but Rarely Present

1/200 of Those Investigated

Pheochromocytoma Not Difficult to Find

Majority > 4 cm, Round, HU > 20

Paraganglioma May Take More Investigation



Paraganglioma
Sympathetic Ganglia

Pheochromocytoma
Adrenal Medulla

Petri BJ. Br J Surg 2009; 96:1381-92

Pheochromocytoma / Paraganglioma

Familial Syndromes: 30-40% are Inherited

Multiple Endocrine Neoplasia Type 2A/2B
Von Hippel Lindau Syndrome
Neurofibromatosis Type 1
Succinate Dehydrogenase Mutations

Genetic Testing is Indicated in All Patients

Pheochromocytoma / Paraganglioma

Malignancy Rate: 15-25%

- **Malignant Diagnosis Cannot be Made by Histology**
- **Diagnosis Only Made When Metastases Appear**
- **Some Mutations Predictive (SDH B)**
- **Latency May Be Up To 20 Years**

Hamidi O. J Clin Endocrinol Metab 2017; 102:3296-3305

Pheochromocytoma / Paraganglioma

Which Hypertensive Patients Should Be Screened?

- **Headaches, Sweating, Palpitations**
- **Severe or Resistant Hypertension**
- **Familial Syndrome**
- **Adrenal Incidentaloma with HU > 10**

Pheochromocytoma / Paraganglioma

Diagnostic Tests

	Sporadic	Hereditary
Test	Sensitivity / Specificity	Sensitivity / Specificity
Plasma Metanephrine	99% / 82%	97% / 96%
Urine Metanephrine (24H)	97% / 45%	96% / 82%
Plasma Catecholamine	92% / 72%	69% / 89%
Urine Catecholamine (24H)	91% / 75%	79% / 96%
VMA (24H)	77% / 86%	46% / 99%

Best Tests
Plasma Metanephrine
Urine Metanephrine (24H)

Adapted from: Lenders JW, JAMA 2002;287:1427-34

Pheochromocytoma / Paraganglioma

Diagnostic Tests – True Positives

Plasma Metanephrine

2-4 Fold > Ref Range

Urine Metanephrine

3-5 Fold > Ref Range

Pheochromocytoma / Paraganglioma

Diagnostic Tests – False Positives

Mild Elevations

Especially Common

Mildly ↑ Norepinephrine

Mildly ↑ Normetaneprine

Pheochromocytoma / Paraganglioma

False Positive Tests – Medications

	Plasma		Urine	
Drug	NMN	MN	NMN	MN
MAO Inhibitors	++	++	++	++
Cocaine	++	+	++	+
Acetaminophen	++	--	++	--
Methyldopa	++	--	++	--
Phenoxybenzamine	++	--	++	--
Sulfasalazine	++	--	++	--
Tricyclics	++	--	++	--
Levodopa	+	+	++	+
Sympathomimetics	+	+	+	+
Buspirone	--	++	--	++
Labetalol	--	--	++	++
Sotalol	--	--	++	++

Pheochromocytoma / Paraganglioma

False Positive Tests

Other Medications and Situations That May Cause False Positives

- Serotonin Norepinephrine Reuptake Inhibitors
- Selective Serotonin Reuptake Inhibitors
- Ethanol Abuse and Withdrawal
- Clonidine Withdrawal

Adrenal Masses

CT Imaging

Benign Conditions

	NCCT	CCT	DCECT	RWP
Adenoma	< 10 HU	Enhances	< 30 HU	> 50%
Pheochromocytoma	> 20 HU	Indeterminate	> 30 HU	< 50%
Myelolipoma	Visible Fat	Visible Fat	Visible Fat	

NCCT = Non Contrast CT – HU
CCT = Contrast CT
DCECT = Delayed Contrast Enhanced CT
RWP = Relative Washout Percentage

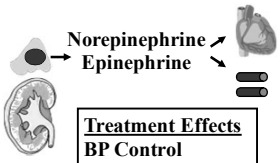
Pheochromocytoma / Paraganglioma

Treatment

Pre-Operative
Alpha Blocker (1st)
Beta Blocker (2nd) or
Calcium Channel Blocker

Then

Adrenalectomy

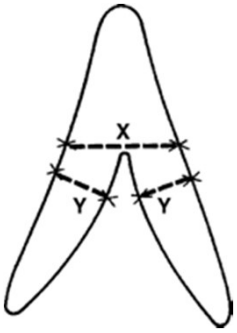


Treatment Effects
BP Control
Volume Expansion
Vasodilation
Rate Control

Paraganglioma Surgery

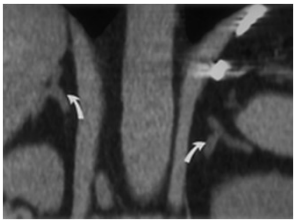
Adrenal Imaging

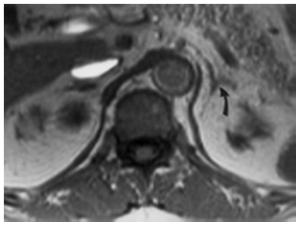
Normal Adrenal Glands



- Normal body size (X): 5-8 mm
- Normal limb size (Y): 2-3 mm
- Total gland width: 2-3 cm

Normal Adrenal Glands





Adrenal Imaging

Lipid Content

CT Scan (Non-Contrast) – Hounsfield Units (HU)

- **Low HU: High Lipid Content = Benign**
  - **Non-Functioning Adenoma**
  - **Cortisol Producing Adenoma**
  - **Aldosterone Producing Adenoma**
- **High HU: Low Lipid Content = Benign or Malignant**
  - **Lipid Poor Adenoma**
  - **Pheochromocytoma**
  - **Adrenal Carcinoma**
  - **Metastatic Carcinoma**
- **MRI: Signal Drop Out = Benign**

Adrenal Imaging

Evaluation

- **Low HU: High Lipid Content = Benign**
  - **Overnight 1 mg Dexamethasone Suppression Test**
  - **Plasma Aldosterone and Renin**
- **High Low Lipid: High HU = Benign or Malignant**
  - **Overnight 1 mg Dexamethasone Suppression Test**
  - **Plasma Aldosterone and Renin**
  - **Plasma Metanephrines**
  - **Examine Image for Features of Carcinoma**
- **MRI: Signal Drop Out = Benign (same as above)**

Case

A 42 year old woman complains of weight gain, fatigue, muscle weakness, and abnormal menses.
Medications: None
Exam: BP 140/90 P 76 Ht 5'4" Wt 155 lb.
Central obesity, facial plethora and rounding, fullness of supraclavicular fat pads, and purple abdominal striae.
Labs: K 3.6 mEq/L, Na 142 mEq/L, Creatinine 0.8 mg/dl

You decide to evaluate for causes of secondary hypertension.

What initial evaluation would have the highest yield?
1. Plasma ACTH
2. AM serum cortisol
3. 24 hour urine cortisol excretion
4. AM serum cortisol and Plasma ACTH

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Central obesity, facial plethora and rounding, fullness of supraclavicular fat pads, and purple abdominal striae.
Labs: K 3.6 mEq/L, Na 142 mEq/L, Creatinine 0.8 mg/dl
Urine cortisol 354 ug/24 hr (nl, 10-60)

What do you recommend now?
1. Plasma ACTH
2. Midnight salivary cortisol
3. MRI pituitary
4. CT abdomen

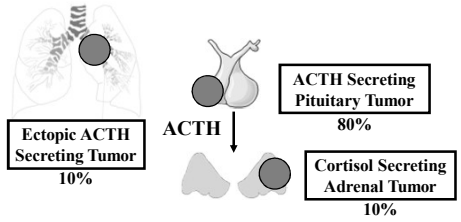
Case 4

A 42 year old woman complains of weight gain, fatigue, muscle weakness, and abnormal menses.
Medications: None
Exam: BP 140/90 P 76 Ht 5'4" Wt 155 lb.
Central obesity, facial plethora and rounding, fullness of supraclavicular fat pads, and purple abdominal striae.
Labs: K 3.6 mEq/L, Na 142 mEq/L, Creatinine 0.8 mg/dl
Urine cortisol 354 ug/24 hr (nl, 10-60)
Plasma ACTH 45 pg/ml (normal: 10-85)

What is the most likely underlying disorder?
1. Ectopic ACTH syndrome
2. Iatrogenic Cushing's syndrome
3. Pituitary ACTH secreting tumor
4. Cortisol producing adrenal adenoma

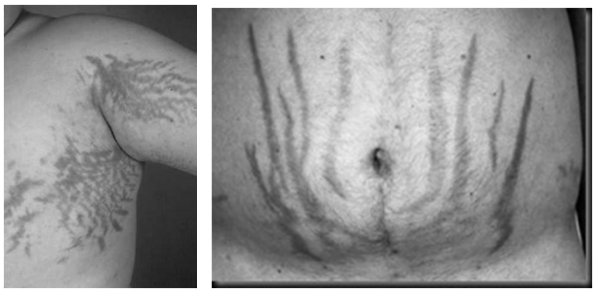
Cushing's Syndrome

Cushing's Syndrome
Endogenous



Cushing's Syndrome
Clinical Features

Cushing's Syndrome
Clinical Features



Cushing's Syndrome
Clinical Features

Cushing's Syndrome
Screening

Screening Tests	Positive Result
▪ 24 Hour Urine Cortisol	Elevated (≥ 2 x nl)
▪ Bedtime Salivary Cortisol	Elevated
▪ 1 mg DST*	Cortisol > 1.8 ug/dl

***DST = Dexamethasone Suppression Test**
Take: 1 mg Dex at 10-11 PM
Measure: serum cortisol next morning at 8:00 AM

Nieman L, J Clin Endocrinol Metab 2008; 93:1526-40
Endocrine Society Clinical Practice Guidelines

Cushing's Syndrome
Differential Diagnosis

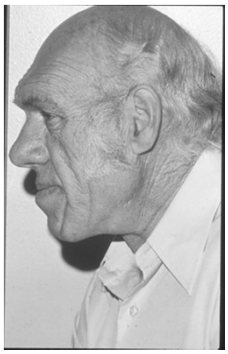
Condition	ACTH (Plasma)	DST (8 mg)
Pituitary ACTH Secreting Tumor	Normal/High	Suppression
Ectopic ACTH Secreting Tumor	High/Very High	No Suppression
Adrenal Cortisol Secreting Tumor	Low	No Suppression

Nieman L, J Clin Endocrinol Metab 2008; 93:1526-40
Endocrine Society Clinical Practice Guidelines

Acromegaly

Acromegaly
Clinical Features

Acromegaly
Clinical Features



Acromegaly
Clinical Features

Acromegaly
Clinical Features

- **Hypertension: Resistant to Therapy**
- **CVD/CHF Mortality: Very High**

Acromegaly. Clinical Practice Guidelines – Endocrine Society
Katznelson L. J Clin Endocrinol Metab 2014; 99: 3933-51

Acromegaly
Diagnostic Testing

- **IGF-1: Elevated - Best Overall Test**
- **GH During OGTT: Failure to Suppress GH**

Acromegaly. Clinical Practice Guidelines – Endocrine Society
Katznelson L. J Clin Endocrinol Metab 2014; 99: 3933-51

Hyperthyroidism

Hypothyroidism

Thyroid Disorders

Hypertension

Hyperthyroidism

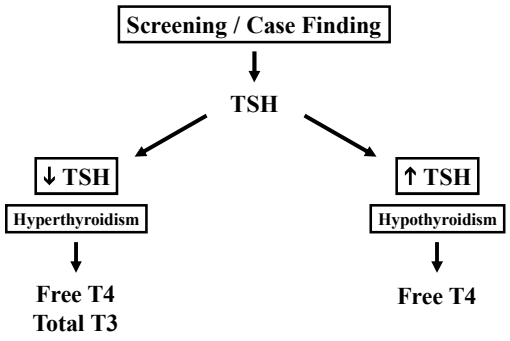
- **Systolic Hypertension**

Hypothyroidism

- **Diastolic Hypertension**

McDermott MT. Ann Intern Med 2009; 151 (11):ITC61
McDermott MT. Ann Intern Med 2012; 157:ITC-1-14.

Thyroid Function Testing



McDermott MT. Ann Intern Med 2009; 151 (11):ITC61
McDermott MT. Ann Intern Med 2012; 157:ITC-1-14.

Thank You