Secondary Hypertension: Clinical Syndromes, Diagnostic Work-up and Management

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DISCLOSURE OF FINANCIAL RELATIONSHIPS

- Grants: NIH/NIDDK and Amgen
- Consultant: Medi Beacon
- Honorarium: ASN
- Off-label usage: None

OBJECTIVES

After the presentation, the attendee will be able to:
1. Describe the clinical clues for secondary forms of hypertension (HTN)
2. State the underlying renal pathophysiology which contributes to the different causes of secondary HTN
3. Recognize the appropriate metabolic and genetic evaluations for patients at risk for secondary HTN
4. Identify disease-specific therapies

Overview of secondary hypertension

- Renal:
  - Renal parenchymal disease
  - Renovascular hypertension (RVHT)
  - Renin secreting tumors
- Adrenal:
  - Primary aldosteronism (PA)
  - Syndromes of mineralocorticoid excess
    - Phaeochromocytoma (PHED)
    - Cushing’s
- Hormonal:
  - Thyroid disorders
  - Primary hyperparathyroidism
    - Acromegaly
- Genetic mutations:
  - Liddle’s
  - Gordon’s
- Drug-induced
- Sleep apnea

ARS:
The most common ‘form’ of secondary hypertension is:

A. Phaeochromocytoma
B. Aldosterone-producing adenoma
C. Renovascular hypertension
D. Coarctation of the aorta
E. Parenchymal renal disease

Features of “Inappropriate” Hypertension...

- Age of onset: <20 or >50 years
- Level of blood pressure: >180/110 mmHg
- Organ damage
  - Fundoscopy: moderate or malignant
  - Serum creatinine >1.5 mg/dL
  - Cardiomegaly or left ventricular hypertrophy (LVH) as determined by electrocardiography
- Presence of features indicative of secondary causes
  - Unproved hypokalemia
  - Abdominal bruit
  - Variable pressures with tachycardia, sweating, menur
  - Family history of renal disease
- Poor response to generally effective therapy
CKD is the most common form of secondary hypertension

- Historical view:
  - 4429 patients referred to resistant hypertension clinic from 1978 to 1993
  - ~10% had identified forms of secondary hypertension
- Hypertension resistance:
  - Patient
  - Physician
  - Disease

SECONDARY CAUSES OF RESISTANT HYPERTENSION

<table>
<thead>
<tr>
<th>Cause</th>
<th>Estimated Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal parenchymal disease</td>
<td>1.0 – 8.0</td>
</tr>
<tr>
<td>Renal artery disease</td>
<td>3.0 – 4.0</td>
</tr>
<tr>
<td>Aldosteronism</td>
<td>1.5 – 15.0</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Cushing's syndrome</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Hyperthyroidism or hypothyroidism</td>
<td>1.0 – 3.0</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>NA</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>&lt;1.0</td>
</tr>
</tbody>
</table>

ARK 22-yr-old woman college student

Hypertensive on THREE antihypertensive agents:
- Labs: 138 102 9 3.3 0.7 0.7 (normal)
- Resting PRA 44 (nl: 1.5-4); aldosterone 27 ng/dL (nl: 2-16)

Which of the following is the most consistent diagnosis?
A. Primary HTN
B. Primary aldosterone excess
C. Bilateral renovascular HTN (FMD)
D. Renin secreting tumor
E. Parenchymal renal disease

Renin-secreting tumor

- Prevalence: very rare
- Mechanism: renin-secreting tumor of JG cells producing pure form of angiotensin-induced HTN (other sources include ovary and testes)
- Presentation: severe HTN with hypokalemia hyperreninemia, hyperangiotensin II and hyperaldosteronism
- Diagnosis: MRA and renal angiogram
- Management:
  - ACE inhibitors and ARB receptor antagonists improve BP
  - Definitive therapy is tumor excision
Aortic coarctation

- Prevalence: ~7% of congenital heart disease, 2-5 X more in males
- Mechanism: activated RAAS
  - Blockage in aortic lumen, usually distal to the left subclavian artery
  - Less commonly, proximal to left subclavian artery = Δ BP in arms
- Presentation: often asymptomatic in adolescence, HTN in the arms with ↓ femoral pulses. CHF >50, 75% die by age 40 and 90% by age 60
- Diagnosis: measurement of BP in arms and legs, interscapular murmur, CXR shows notching of posterior ribs 3-8 and “3” sign of aorta with pre and post-stenotic dilatation. CT, MRA, echocardiography, and aortography are all useful.
- Management: surgery (and angioplasty) for patients with transtenotic gradient >30 mmHg. HTN cure is age dependent.
  - 90% cure if corrected in childhood; <50% after age 50

Pheochromocytoma

- Frequently sought, rarely found (<< 0.1% of hypertensives)
- When correctly diagnosed and properly treated, it is curable
- When undiagnosed or improperly treated, it can be fatal

Clinical Clues for Pheochromocytoma (PHEO)

- Hyperadrenergic spells
- Resistant hypertension, especially in the young with pressor response to anesthesia, stress, etc.
- Adrenal “incidentaloma”
- Familial syndromes
  - VHL, MEN-2, NF-1, SDH

Signs & symptoms of PHEO

- Hypertension (probably >90%)
  - Paroxysmal (50%)
  - Sustained (30%)
  - Paroxysms superimposed (~ 50%)
  - Hypotension, orthostatic (10% - 50%)
- Headache (40% - 80%)
- Excessive sweating (40% - 70%)
- Palpitations and tachycardia (45% - 70%)
- Pallor (40% - 45%)
- Anxiety and nervousness (20% - 40%)

Pheochromocytoma (PHEO)

**Diagnostic Considerations**

- If a PHEO is responsible for “classic spells,” then the biochemical test results are always unequivocally abnormal.
- Overtly symptomatic patients with plasma catecholamines (NE+E) >1000 pg/ml or plasma MN <0.9 and/or MN <0.5 nmol/L DO NOT HAVE PHEO
- PHEO patients may be completely asymptomatic yet may have elevated circulating catecholamines
- With widespread use of CT and MRI approximately 50% of all PHEO are initially detected as adrenal incidentalomas in patients without spells and frequently without hypertension

Catecholamine Metabolism

<table>
<thead>
<tr>
<th>Tyrosine</th>
<th>Tyrosine Hydroxylase</th>
<th>Dopamine</th>
<th>L-Dopa</th>
<th>Dopamine β-hydroxylase</th>
<th>Phenylethanolamine N-methyltransferase</th>
<th>Epinephrine</th>
</tr>
</thead>
<tbody>
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<td>Phenylethanolamine N-methyltransferase</td>
<td>Epinephrine</td>
</tr>
</tbody>
</table>

Phenol have large amounts of COMT

NMN, MN circulate freely in plasma, sulfated in GI circulation and excreted in urine

**Simplified Algorithm for the Biochemical Testing of Suspected Pheochromocytoma**

**Clinical suspicion of pheochromocytoma**
- MN > 1.21 nmol/L, NMN > 2.21 nmol/L
- Catecholamines > 2000 pg/mL
- Urinary (MN + NMN) > 1.8 mg/24 h

**Positive**
- Clonidine suppression test
  - Plasma catecholamines increased at least 3-fold from baseline and >2000 pg/mL at 1 or 2 min after IV bolus of glucagon (2.0 mg)

**Negative**
- Clonidine suppression test: no change in plasma catecholamines
- MN < 0.5 nmol/L, NMN < 0.9 nmol/L
- Catecholamines < 1000 pg/mL
- Urinary (MN + NMN) < 1.3 mg/24 h

**MN=metanephrine levels; NMN=normetanephrine levels**

**Pharmacologic testing for PHEO**

A. Glucagon stimulation
- Indicated in patients with suggestive clinical manifestations but catecholamine production is equivocal (i.e., plasma catecholamines < 1000 pg/mL and/or total urinary MN + NMN < 1.8 mg/24 h)
- Positive test: 3- to 10-fold increase in plasma catecholamines at least 3-fold from baseline and ≥2000 pg/mL at 1 or 2 min after IV bolus of glucagon (2.0 mg)

B. Clonidine suppression test
- Used to separate patients with neurogenically-mediated catecholamine release
- Indicated for those patients with plasma catecholamines between 1000 or 2000 pg/mL
- Normal response: ≥50% decrease in plasma catecholamines 2 to 3 hrs after oral administration of 0.3 mg clonidine

**Medications That Can Cause False-Positive Elevations of Plasma and Urinary Catecholamines or Metanephrines**

<table>
<thead>
<tr>
<th>Medications</th>
<th>Catecholamines</th>
<th>Metanephrines</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE</td>
<td>E</td>
<td>NMN</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>+++</td>
<td>—</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>+++</td>
<td>—</td>
</tr>
<tr>
<td>Labetalol*</td>
<td>+++</td>
<td>—</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Caffeine</td>
<td>++</td>
<td>—</td>
</tr>
<tr>
<td>Levodopa, Carbidopa</td>
<td>++</td>
<td>—</td>
</tr>
<tr>
<td>Cocaine</td>
<td>++</td>
<td>—</td>
</tr>
<tr>
<td>Acetaminophens*</td>
<td>++</td>
<td>—</td>
</tr>
<tr>
<td>Buspirone*</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* cause biochemical interference

**Location of pheochromocytoma**

<table>
<thead>
<tr>
<th>Location</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-abdominal</td>
<td>95</td>
</tr>
<tr>
<td>Single adrenal tumor</td>
<td>50 – 70</td>
</tr>
<tr>
<td>Single extra-adrenal tumor</td>
<td>10 – 20</td>
</tr>
<tr>
<td>Multiple tumors*</td>
<td>15 – 40</td>
</tr>
<tr>
<td>– Bilateral adrenal tumors</td>
<td>5 – 25</td>
</tr>
<tr>
<td>– Multiple extra-adrenal tumors</td>
<td>5 – 15</td>
</tr>
<tr>
<td>Outside the abdomen</td>
<td>5</td>
</tr>
<tr>
<td>– Intrathoracic</td>
<td>2</td>
</tr>
<tr>
<td>– In the neck</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

* More common in children and in familial syndromes

**Adrenal CT Scan of a Pheochromocytoma**

- Dense, vascular, inhomogeneous, HU > 22, contrast washout < 50%

Sensitivity: 98%
Specificity: 70%
PV (+): 69%
PV (-): 98%

When to obtain a $^{123}$I-MIBG:
- Positive biochemistry but negative CT/MRI
- >10-cm adrenal mass
- Extra-adrenal mass

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**$^{123}$I-MIBG Scintigraphy for the Detection of Pheochromocytoma: Results of a Meta-analysis**

- No. of subjects with confirmed disease: 395
  Sensitivity = 94% (95% CI, 91-97%)
- No. of disease-free subjects: 370
  Specificity = 92% (95% CI, 87-98%)

(J Clin Endocrinol Metab 2010;95:2596.)

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**Familial syndromes with PHEO**

<table>
<thead>
<tr>
<th>Type</th>
<th>Tumors (partial list)</th>
<th>Site of genetic mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple endocrine neoplasia 2A (MEN 2A)</td>
<td>Medullary thyroid carcinoma, PHEO, hyperparathyroidism</td>
<td>Chromosome 10q11.2, codon 634, Cys → Arg in 85%</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia 2B (MEN 2B)</td>
<td>Medullary thyroid carcinoma, PHEO, mucosal neuromas</td>
<td>Chromosome 10q11.2, codon 918, Met → Thr in 95%</td>
</tr>
<tr>
<td>von Hippel–Lindau, type 2 (VHL-2)</td>
<td>PHEO (15-20%), Retinal angiomata, CNS hemangioblastoma, Renal cysts + carcinoma, Neuroendocrine tumors</td>
<td>Chromosome 3p25-26, codon 167 in 40%</td>
</tr>
<tr>
<td>von Recklinghausen's disease (neurofibromatosis 1)</td>
<td>Neurofibroma, Optic glioma, PHEO (10%), Carotid tumors</td>
<td>Chromosome 17q11.2 in 90%</td>
</tr>
</tbody>
</table>


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**Management of pheochromocytoma (PHEO)**

- **DRUGS**
  - Phenoxybenzamine:
    - non-specific α-blocking agent
    - not well tolerated because of severe orthostatic hypotension
    - tachycardia, diarrhea, and contributes to severe hypotension following tumor removal
  - Calcium antagonists:
    - effective vasodilators
    - well tolerated
  - α - adrenergic antagonists:
    - specific postganglionic α-blocking agents
  - β-blockers:
    - useful in the presence of cardiac arrhythmias
  - should be used only AFTER adequate α-blockade
  - α, β-blockers (labetalol)

- **SURGERY** Life-time follow-up
ARS
A 29-yr-old woman with untreated BP of 162/102 mmHg, no family history of HTN, and normal exam.

LABS:

<table>
<thead>
<tr>
<th>138</th>
<th>102</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3</td>
<td>28</td>
<td>0.7</td>
</tr>
</tbody>
</table>

U/A normal

WHAT WOULD YOU DO NEXT?
A. Plasma aldosterone (PA), plasma renin activity (PRA)
B. Plasma metanephrines
C. Sleep study
D. Renal angiogram
E. None of these things

Primary Aldosteronism

Population at Risk for Primary Aldosteronism

- Spontaneous or unprovoked hypokalemia (K⁺ ≤ 3.5 mEq/L)
- Severe diuretic-induced hypokalemia (K⁺ < 3.0 mEq/L)
  - Does not normalize after discontinuation of diuretics for at least four (4) weeks
- Have resistant hypertension with no other evidence of a secondary cause
- Hypertension with adrenal adenoma
- Family history of primary aldosteronism

Primary Aldosteronism

- Prevalence: may be 5% (or more)
- Mechanism: excessive secretion of aldosterone due to adenoma or bilateral adrenal cortical hyperplasia
- Presentation: hypokalemia, metabolic alkalosis and drug-resistant hypertension
- Diagnosis:
  - Document renal K wasting
  - Plasma aldosterone/renin ratio >20 is suggestive
  - 24-hr urine aldosterone >14 µg on 250 mEq Na x 3 days
  - Abdominal CT helpful, if adenoma is found
- Treatment:
  - Spironolactone or eplerenone effective
  - Surgical “cure” possible

Supine Serum Potassium Values After Five Days on 150 mEq Sodium Intake per 24 hr

From: Bravo EL and coworkers. AJM April 1983

Normal Physiology

Adrenal Cortex

Mineralocorticoid receptors

Aldosterone synthase

Angiotensinogen

AngII

ACE

ACTH

Mineralocorticoid receptors

aldosterone synthase

aldosterone

normal ECV hypokalemia
Primary Aldosteronism

Adrenal Cortex

Hemodynamics of Primary Aldosteronism

MAP: mean arterial pressure, CI: cardiac index, TPR: total peripheral resistance, PV: plasma volume. Cross-hatched areas indicate 95% CI.


CONTROVERSIES (1)

Plasma Aldosterone:Plasma Renin Activity (PA:PRA) Ratio

- PA:PRA is highly sensitive but has a high false positive rate of 35% to 50%.
- Wide variation in sensitivity (64% to 100%) and specificity (87% to 100%)
- Reported ratios are all laboratory-dependent (especially low PRA)
- Proper preparation
  - Restore serum K+
  - Blood-pressure medications acceptable including ACE/ARB, diuretic, adrenergic inhibitor
  - Hold MR antagonists for 2 weeks

CONTROVERSIES (2)

Plasma Aldosterone:Plasma Renin Activity (PA:PRA) Ratio

- Better diagnostic accuracy is obtained if the absolute plasma aldosterone concentration is included as a second criterion in combination with PA:PRA ratio.
- The combination of a PA:PRA ratio >30 and a PA value >20 ng/dL had a sensitivity of 90% and specificity of 91% for APA (Weinberger 1993)
- A PA:PRA ratio ≥20 and PA ≥15 ng/dL were found in >90% of patients with surgically-confirmed APA (Young 1999)

CONTROVERSIES (3)

PA:PRA ratio in the evaluation of primary aldosteronism

- Mainly a reflection of the level of PRA and does not reflect aldosterone autonomy (Montori et al. Mayo Clin Proc 2001;76:877)
- Lacks sensitivity and specificity and primarily reflects the level of PRA which usually falls with age and is not associated with aldosterone excess. (Schwartz et al. Am J Hypertens 2002)
- PA:PRA ratio is a screening test suggestive of primary aldosteronism

Drugs affecting renin/aldosterone

<table>
<thead>
<tr>
<th>PRC</th>
<th>PRA</th>
<th>Aldosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>ARB</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Direct renin inhibitors</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Aldo receptor blockers</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
% Primary Aldosteronism

JNC VI:


Biochemical confirmation of primary aldosteronism:
non-suppressible aldosterone excretion rate after 3 days of sodium loading (250 mEq Na per 24 hr)

Clinical utility of some biochemical measurements in the diagnosis of primary aldosteronism

An Approach to Patients at Risk for Primary Aldosteronism

CT Scan of an Adrenal Adenoma

Primary aldosteronism: left adrenal adenoma

Bilateral Adrenal Venous Sampling

<table>
<thead>
<tr>
<th>Venous site</th>
<th>Aldosterone (ng/dL)</th>
<th>Cortisol (µg/dL)</th>
<th>A/C ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left adrenal</td>
<td>11,500</td>
<td>786</td>
<td>15.33</td>
</tr>
<tr>
<td>Right adrenal</td>
<td>1,200</td>
<td>750</td>
<td>1.53</td>
</tr>
<tr>
<td>Low IVC</td>
<td>43</td>
<td>25</td>
<td>1.72</td>
</tr>
</tbody>
</table>

- Left adrenal vein A/C ratio divided by R adrenal vein A/C ratio = 10 (value >4 indicates lateralization to left adrenal)
- Right adrenal vein A/C ratio divided by low IVC A/C ratio = 0.89 (value <1.0 indicates suppression of aldosterone secretion from the right adrenal)
Primary Aldo.: MEDICAL TREATMENT

- MR antagonist starting dosages:
  - Spironolactone 25 mg once daily
  - Eplerenone 25 mg twice daily
- Dose titration
  - Increase dose by 25 mg every 2 weeks as needed
  - Treatment goal: mid-top high-normal serum potassium without the aid of oral potassium supplement – unlike other BP meds, the treatment goal is not BP-driven
- Add-on agents – start with a thiazide diuretic, CCB

Predictors of HTN cure after adrenalectomy in primary aldosteronism

- 97 adrenalectomies for primary aldosteronism (33% cure rate)
- Cure of HTN after adrenalectomy independently associated with:
  1. Lack of family history of HTN
  2. Preoperative use of ≤2 antihypertensive agents
  3. Youth and shorter duration of HTN


Glucocorticoid-responsive aldosteronism (GRA)

- Etiology: acquisition of aldosterone synthase activity by cortisol-producing zona fasciculata
- Clues: early onset HTN and hypokalemia
  - Strong family history of early HTN often associated with early death due to CVA
  - Family history of aldosteronism
- Diagnosis: suppressed PRA and ↑PA, ↑18-OH cortisol, ↑ACTH & ↑18-oxo-cortisol
  - Direct genetic testing for crossover between aldo-synthase and 11β-hydroxylase
- Treatment:
  - Suppression of ACTH by dexamethasone
  - Mineralocorticoid receptor blockade with SPLOT
  - Inhibition of the mineralocorticoid-sensitive distal tubule sodium channel with amiloride


Glucocorticoid remedial hypertension

- A 23-yr-old man with drug-resistant HTN and positive family history of hypertension:
  - On 40 mg lisinopril and 10 mg amiodipine and a K supplement, BP is still 162/96 mmHg...detailed physical exam normal
  - Labs: 138 100 10 3.1 28 0.8
  - Renin is 0.2 ng/mL/hr and aldosterone is 3 ng/dL
WHAT IS THE NEXT STEP?

A. Genetic testing
B. Complex metabolic testing
C. Read more
D. All of the above

Liddle’s syndrome:

- **Prevalence:** < 0.1 % hypertensives
- **Mechanism:**
  - Autosomal dominant activating mutation(s) in epithelial sodium channel (ENaC) of the collecting duct.
  - Impaired regulatory mechanism leads to an ↑ number of ENaC channels on luminal membrane
- **Presentation:** severe salt sensitive HTN, marked hypokalemia, low renin and low aldosterone
- **Diagnosis:** clinical DX can be confirmed by genetic analysis of ENAC gene
- **Treatment:**
  - Responds to low Na+ diet, amiloride
  - Cured by renal transplant

### Liddle’s syndrome

**Normal**

**Pathogenesis**

<table>
<thead>
<tr>
<th>Urine</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Cell</td>
<td>ENac</td>
</tr>
<tr>
<td>Aldosterone receptors</td>
<td>ENac</td>
</tr>
<tr>
<td>Hyponatremia &amp; Hypokalemia</td>
<td>ECV</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
</tbody>
</table>

### Apparent Mineralocorticoid Excess Syndromes

**11-β deficiency (11-β HSD2)**

- **Etiology:** normally, 11-β converts cortisol to inactive cortisone, protecting mineralocorticoid receptor from cortisol and allowing selective access for aldosterone. When 11-β-dehydrogenase is defective, e.g., in congenital deficiency or after licorice administration, cortisol gains access to mineralocorticoid receptors, resulting in sodium retention and renal potassium wasting
- **Presentation:** HTN, hypokalemia
- **Diagnosis:** low aldosterone, suppressed PRA, increased ratio of urinary cortisol to cortisone metabolites
- **Treatment:** glucocorticoids to suppress ACTH; SPST to block mineralocorticoid receptors.

**Normal Kidney**

<table>
<thead>
<tr>
<th>CORTISOL</th>
<th>CORTISONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALDO</td>
<td></td>
</tr>
</tbody>
</table>

**AME Kidney**

<table>
<thead>
<tr>
<th>CORTISOL</th>
<th>CORTISONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALDO</td>
<td></td>
</tr>
</tbody>
</table>

Disorder (D=dominant, Mutant Gene

**Inherited renal tubular disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Consequence of Mutant Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN and hypokalemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoid-remediable aldosteronism (GRA) (familial hyper-aldosteronism, type I)</td>
<td>R</td>
<td>Increased activity of mineralocorticoid receptor</td>
</tr>
<tr>
<td>Apparent mineralocorticoid excess</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation of mineralocorticoid receptor</td>
<td>D</td>
<td>Increased activity of epithelial sodium channel</td>
</tr>
<tr>
<td>Liddle's syndrome</td>
<td>D</td>
<td>Increased activity of epithelial sodium channel</td>
</tr>
</tbody>
</table>


**Gordon’s syndrome:**

Pseudohypoaldosteronism type 2

- **Prevalence:** very rare
- **Mechanism:** gain of function mutations in WNK1 (serine-threonine) kinases leading to ↑-NaCl reabsorption, impaired K excretion and hyporeninemic hypoaldosteronism
- **Presentation:** autosomal dominant inheritance. Moderate to severe HTN with hyperkalemia and hyperchloremic acidosis, normal GFR
- **Diagnosis:** clinical DX. Genetic testing not widely available
- **Management:** low-salt diet and thiazide diuretic


**Clinical evaluation of an incidental adrenal mass (n=2005)**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
<th>Suggestive clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing syndrome</td>
<td>7.9%</td>
<td>Weight gain, metabolic syndrome (glucose intolerance, dyslipidemia, central obesity) PLUS supravacuicular fat pads, facial plethora, easy bruising, purple striae, proximal muscle weakness, emotional and cognitive changes, opportunistic infections, altered reproductive function, acne, hirsutism, osteoporosis, and leukocytosis with lymphopenia</td>
</tr>
<tr>
<td>PHACE</td>
<td>5.6%</td>
<td>HTN (Paroxysmal or sustained) PLUS spells of sweating, headache, palpitations, and pallor</td>
</tr>
<tr>
<td>T1-Aldo</td>
<td>1.2%</td>
<td>Refractory HTN with or without hypokalemia</td>
</tr>
<tr>
<td>Adrenocortical carcinoma</td>
<td>1.6%</td>
<td>Abdominal pain (mass effect), Cushing syndrome (cortisol effect), virilization (androgen effect), hyperesosinophilia (estrogen effect), and hypokalemia (aldosterone effect)</td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>2.5%</td>
<td>History of extra-adrenal cancer, cancer-specific signs</td>
</tr>
</tbody>
</table>


**Definiton: Adrenal incidentaloma**

- **An adrenal mass discovered serendipitously** by radiologic examination
- **In the absence of symptoms or clinical findings suggestive of adrenal disease**
- **And > 1-cm in diameter**
Typical imaging features (phenotype) of incidental adrenal masses

<table>
<thead>
<tr>
<th>Feature</th>
<th>Adrenal adenoma</th>
<th>Adrenocortical carcinoma</th>
<th>PhEo</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Small (&lt;3 cm)</td>
<td>Large (&gt;4 cm)</td>
<td>Large (&gt;3 cm)</td>
<td>Variable</td>
</tr>
<tr>
<td>Laterality</td>
<td>Unilateral, solitary</td>
<td>Unilateral, solitary</td>
<td>Unilateral, solitary</td>
<td>Often bilateral</td>
</tr>
<tr>
<td>Unenhanced CT density (HU)</td>
<td>≤ 10</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Contrast-enhanced CT</td>
<td>Not vascular</td>
<td>Hyperintense</td>
<td>Markedly hyperintense</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>MRI (Relative to liver on T2-weighted imaging)</td>
<td>Isointense</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Growth rate</td>
<td>Stable or slow (&lt;1 cm/yr)</td>
<td>Rapid (&lt;2 cm/yr)</td>
<td>Slow (0.5-1.0 cm/yr)</td>
<td>Variable</td>
</tr>
</tbody>
</table>


Obstructive Sleep Apnea (OSA) & HTN

- OSA and HTN commonly co-exist...
  - About 50% of patients with OSA are hypertensive
  - About 30-40% of HT patients have OSA
- High AH is associated with greater likelihood of HTN (WSCS/SHHS)
- Pathophysiologic mechanisms
- CPAP therapy – modest BP effect (2 – 5 mmHg)


Pathophysiologic mechanisms in the etiology of OSA

- **Hypoxemia/reoxygenation**
- **Hypercapnia**
- **Arousals/sleep fragmentation**
- **Increase in intrathoracic pressure**

HTN risk factors:
- Obesity
- Older age
- High salt diet
- Hyperaldosteronism
- African American race
- Sedentary lifestyle
- Kidney disease

OSA physiologic effects:
- Sympathetic activation
- Oxidative stress
- Inflammation
- Endothelial dysfunction
- Vascular stiffening
- RAAS activation

Nocturnal arterial HTN

Sustained arterial HTN

Summary of meta-analyses of randomized controlled CPAP trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of trials/patients</th>
<th>BP end point</th>
<th>Minimum CPAP duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alipari et al. 16/587</td>
<td>Office/ambulatory 4 wk</td>
<td>SBP: -2.5 mm Hg (not significant)</td>
<td>More benefit in more severe OSA treated for better SBP reduction with better CPAP adherence</td>
<td></td>
</tr>
<tr>
<td>Alipari et al. 16/587</td>
<td>Office/ambulatory 4 wk</td>
<td>DBP: -1.7 mm Hg (not significant)</td>
<td>More benefit in more severe OSA treated for better SBP reduction with better CPAP adherence</td>
<td></td>
</tr>
<tr>
<td>Besier et al. 16/587</td>
<td>Office/ambulatory 2 wks</td>
<td>SBP: -1.2 mm Hg</td>
<td>More benefit in patients with higher baseline SBP, higher BMI, and more severe OSA</td>
<td></td>
</tr>
<tr>
<td>Besier et al. 16/587</td>
<td>Ambulatory 7 wks</td>
<td>SBP: -1.5 mm Hg</td>
<td>More benefit in patients with higher baseline SBP, higher BMI, and more severe OSA</td>
<td></td>
</tr>
<tr>
<td>Besier et al. 16/587</td>
<td>Ambulatory 7 wks</td>
<td>DBP: -1.5 mm Hg</td>
<td>More benefit in patients with higher baseline SBP, higher BMI, and more severe OSA</td>
<td></td>
</tr>
<tr>
<td>Mo and He 7/471</td>
<td>Ambulatory 4 wks</td>
<td>SBP: -0.9 mm Hg (not significant)</td>
<td>DBP: -1.8 mm Hg</td>
<td></td>
</tr>
</tbody>
</table>

BMI = body mass index; BP = blood pressure; CPAP = continuous positive airway pressure; DBP = diastolic blood pressure; OSA = obstructive sleep apnea; SBP = systolic blood pressure


QUESTIONS?