A practical approach to diagnosis and management of primary aldosteronism

Irina Bancos
Objectives

• Describe a practical approach to making the diagnosis of primary aldosteronism (PA)
• Review interpretation of Adrenal vein sampling
• Compare surgical versus medical therapy for primary aldosteronism
• Identify gaps in management of primary aldosteronism
49 YO man with hypertension

- Hypertension for 10 years
- Several episodes of hypokalemia

**Medications:**
- Amlodipine 10 mg daily
- Benazepril 40 mg daily
- Spironolactone 25 mg daily
- Potassium 120 mEq daily

- Blood pressure: 145/98

**Family history:** hypertension in mother and 2 brothers (onset at older age)
Epidemiology and presentation of Primary Aldosteronism

• **Prevalence:**
  – 5-10% in patients with hypertension
  – 15-20% in patients with treatment-resistant hypertension

• **Why care?**
  – **Cardiovascular morbidity and mortality rates** in PA are increased to essential hypertension (matched for age, sex and blood pressure)
  – **Impaired physical and mental quality of life**
  – Potentially surgically curable disease

Clinical presentation

• Adults: between 20s and 60s years of age
  – Median 54 years old (21-86)*
  – Gender: 36% women, 64% men*

• Hypertension
  – APAs tend to have higher aldosterone levels and higher blood pressures than patients with IHA
  – The mean blood pressure was 184/112 mmHg in the first 262 patients with PA who were diagnosed at Mayo Clinic (1957–1986)
  – The mean blood pressure was 141/87 mmHg in the last 407 patients with PA (2014-2019), treated with a median of 3 antihypertensive agents

*Adrenal database (Mayo Clinic, 2000-2019)
Clinical presentation

• **Polyuria and nocturia** (hypokalemia-induced renal-concentrating defect)

• **Hypokalemia** is present in:
  – around 30% of patients with PA (unchanged with time)
  – 70% of patients undergoing adrenalectomy for unilateral disease

• Deep-seated **renal cysts** are found in 40-60% of patients with PA who have chronic hypokalemia

• **Sodium** tends to be high–normal or slightly above the upper limit of normal

*Adrenal database (Mayo Clinic, 2000-2019)
Comorbidities in untreated primary aldosteronism

• **Meta-analysis of 31 studies:** (3838 patients with PA vs 9284 patients with essential hypertension) →
  - **Stroke:** OR 2.58
  - **Coronary artery disease:** OR 1.77
  - **Atrial fibrillation:** OR 3.52
  - **Heart failure:** OR 2.05
  - **Diabetes:** OR 1.33
  - **Metabolic syndrome:** OR 1.53
  - **Left ventricular hypertrophy:** OR 2.29

• **Systematic review (15 studies):** negative impact of PA on quality of life
  - impaired physical and mental quality of life compared to the general population
  - Symptoms of **anxiety, demoralization, stress, depression and nervousness** were more frequently reported in untreated patients with PA than in the general population and in patients with hypertension
Should this patient be tested for Primary Aldosteronism?

The Endocrine Society guidelines on PA recommend testing high-risk groups:

1. patients with sustained blood pressure above 150/100 mmHg on each of three measurements obtained on different days
2. patients with hypertension resistant to three conventional antihypertensive drugs (including a diuretic) or controlled blood pressure on four or more antihypertensive drugs;
3. patients with hypertension and spontaneous or diuretic-induced hypokalemia
4. patients with hypertension and adrenal incidentaloma
5. patients with hypertension and sleep apnea
6. patients with hypertension and a family history of early onset hypertension or cerebrovascular accident at a young age (<40 years)
7. all hypertensive first-degree relatives of patients with PA
Guidelines: not followed by physicians

• Survey of 500 general practitioners in Italy and Germany (Mulatero et al, 2016):
  • 3135 patients – 18-25% with hypertension
  • case detection testing for PA: 7–8%
  • Prevalence of PA: 1-2%

  – Population study, Italy (Rossi et al, 2017)
    • 2000-2015, age >20 YO
    • Predicted: 5% of hypertension → Results: 5 times less than predicted
Easy approach to case detection for PA:

Young WF, 2019 J Intern Med
Easy approach to case detection 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)

\[
PAC \geq 277 \text{ pmol/L} \ (\geq 10 \text{ ng dL}^{-1}) \text{ and} \\
\downarrow \text{PRA} \ (<1.0 \text{ ng mL}^{-1} \text{ h}^{-1}) \text{ or } \downarrow \text{PRC} \ (< \text{lower limit of reference})
\]

Confirmatory Testing (if spontaneous \(\downarrow K^+\) absent):
- 24-h urine for aldosterone and sodium on a high sodium diet
- 4-h saline infusion test

OK to perform while on any antihypertensive medications if case detection is positive

Young WF, 2019 J Intern Med
Medications: implications for diagnosis

• Antihypertensive medications
  – can cause **false-negative** results in mild PA
  – Do **NOT** cause **false-positive** results (as long as a cut-off level for aldosterone is used)

• No effect on diagnostic accuracy:
  – Calcium channel blockers
  – Alpha 1-adrenergic receptor blockers

• **Increase renin:**
  – Angiotensin-converting enzyme inhibitors
  – Angiotensin receptor blockers
  – High doses of triamterene or amiloride
  – Mineralocorticoid receptor antagonists - spironolactone and eplerenone

<table>
<thead>
<tr>
<th>Renin is not suppressed:</th>
<th>Renin is suppressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRAs should be stopped for 6 weeks and patient retested</td>
<td>- can proceed with case detection testing, confirmatory testing and AVS</td>
</tr>
</tbody>
</table>
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Young WF, 2019 J Intern Med
Oral sodium loading test

- Preferred test to confirm PA at Mayo Clinic
- **Before the test:** 1) normalize serum potassium and 2) hypertension control
- **Test:**
  - high-sodium diet for 3 days
  - Goal: sodium intake of 5000 mg through diet or or sodium chloride tablets
  - Morning of 3rd day: 24-h urine collection is started
  - Measurements: 24h urine aldosterone, sodium and creatinine
- **Test interpretation:**
  - Patients without PA: when sodium excretion > 200 mEq → renin and aldosterone should be low
  - Patients with PA: urine aldosterone >12 mcg/24 h (in the setting of low renin)

- The sensitivity and specificity of the oral sodium loading test are 96% and 93%, respectively
Intravenous saline infusion test

• **Test:**
  – Following an overnight fast, 0.9% sodium chloride solution (2 L) is infused intravenously over 4 h with the patient in the seated position
  – Heart rate and blood pressure are monitored during the infusion
  – At the completion of the infusion, blood is collected for measurement of aldosterone

• **Test interpretation:**
  – In patients without PA: aldosterone levels decrease to <5ng/dl
  – In patients with PA: **aldosterone levels >10 ng/dl**

• Other confirmatory tests (fludrocortisone suppression and captopril stimulation tests) are not used at Mayo clinic.
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- Blood pressure: **145/98**

**Family history:** hypertension in mother and 2 brothers (onset at older age)

**Aldosterone:** **30** (<21 ng/dl)
**RPA:** **<0.6** ng/ml/h
**Potassium:** **3.6** mmol/l (normal 3.6-5.2 mmol/l)

**Confirmatory testing:** **not performed** (not needed)

**Primary aldosteronism**
Subtype of PA:

- **Goal of subtype testing:** determine source of aldosterone excess - right, left or both adrenal glands

- *Aldosterone-producing adenoma* – usually small <2 cm, PA is usually more severe (vs hyperplasia)

- *Bilateral idiopathic hyperaldosteronism* – micronodular hyperplasia or normal adrenal imaging

- *Unilateral hyperplasia* (micronodular or macronodular hyperplasia of the zona glomerulosa)

- *Familial hyperaldosteronism* – rare

- *Aldosterone-producing carcinoma* - >4 cm, severe PA
Underlying pathology in unilateral PA:

- Retrospective study, Mayo Clinic Rochester
- 2004-2015
- Inclusion criteria: AVS with lateralization, adrenalectomy, post-adrenalectomy biochemical data
- Pathology review: single adenoma, multiple unilateral adenomas, hyperplasia
- 206 patients
  - Single adenoma: 152 (74%)
  - Unilateral hyperplasia: 22 (16%) - more likely men, left site, lower LI
  - Multiple unilateral adenomas: 21 (10%)
Subtype Testing for Primary Aldosteronism

Normal, micronodularity, bilateral masses or atypical unilateral mass (but not ACC)

- Surgery not desired
- Surgery desired

Adrenal CT scan

Unilateral hypodense nodule >1 cm and <2 cm

- Surgery desired
- Surgery not desired

AVS

Medical therapy with a MRA

- No lateralization with AVS
- Lateralization with AVS

Unilateral laparoscopic adrenalectomy

Medical therapy with a MRA

>35 y consider

≤35 y & marked PA, consider
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Primary aldosteronism
Adrenal cross-sectional imaging is not able to distinguish accurately between APA and IHA

- Retrospective study, Mayo Clinic Rochester
- 1993-2011
- Inclusion criteria: AVS with lateralization, unilateral adrenalectomy, follow up data

Lim et al, 2014, JCEM
Patients with follow-up data\(^a\)
\[ n = 143 \]

- Not cured (bilateral disease)\(^b\)
  \[ 4\% \quad n = 6 \]

- Cured (unilateral disease)\(^b\)
  \[ 96\% \quad n = 127 \]

- Unknown status
  \[ n = 10 \]

**AVS concordance: 97%**

**Minimum age of imaging-cure concordance:** 35.1 years

\[ \text{Adenoma diameter, cm} \]
\[ \text{Age, Yr} \]

- Accurate imaging:
  - \(<35\) yrs
  - \(\geq35-40\) yrs
- Inaccurate imaging:
  - \(\geq35-40\) yrs

**Accurate CT or MRI\(^c\)**
\[ n = 77 (59\%) \]

**Inaccurate CT or MRI\(^c\)**
\[ n = 50 (41\%) \]

- Bilateral abnormalities on scan \((n = 48)\)
- Unilateral abnormality on scan but in the opposite adrenal \((n = 2)\)
Adrenal vein sampling

- **Success rate** of circa **97%** (performed by a single experienced radiologist)
- **Complication rate** **2.5%**
- **Protocol at Mayo Clinic**: continuous cosyntropin infusion (50 mcg/h starting 30 min before sampling and continuing throughout the procedure):
  - minimal cortisol gradient cut-off (adrenal-to-IVC) to determine successful catheterizations is **>5 : 1**
  - mean adrenal-to-IVC cortisol: **34 : 1** (R) and **24 : 1** (L)

Adrenal vein sampling: interpretation

• Patients with aldosterone producing adenoma: mean cortisol corrected aldosterone ratio $\geq 4:1$

• Patients with bilateral aldosterone producing hyperplasia: mean cortisol corrected aldosterone ratio $<3:1$

• Mayo Clinic data:
  – Unilateral disease: mean cortisol corrected Aldosterone ratio is $18 : 1$
  – Bilateral disease: mean cortisol-corrected ALR is $1.8 : 1$
Contralateral suppression index (CSI)

- Contralateral (nondominant adrenal) aldosterone/cortisol ratio is divided by the IVC aldosterone/cortisol ratio

- **Aldosterone corrected cortisol ratio is between 3 and 4:**
  - CSI <1.0 is predictive of good surgical outcomes

- **Adrenal vein sampling is not bilaterally successful:**
  - CSI <0.5 is highly predictive of contralateral disease

- **Prediction of postoperative hyperkalemia:**
  - CSI <0.47 : high risk for postoperative hyperkalemia

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<table>
<thead>
<tr>
<th></th>
<th>Cortisol</th>
<th>Aldosterone</th>
<th>Aldosterone/Cortisol</th>
<th>Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVC</td>
<td>27</td>
<td>53</td>
<td>1.96</td>
<td>CSI: 0.53</td>
</tr>
<tr>
<td>RAV</td>
<td>1150</td>
<td>1200</td>
<td>1.04</td>
<td>Left to Right ratio :13.3</td>
</tr>
<tr>
<td>LAV</td>
<td>442</td>
<td>6100</td>
<td>13.8</td>
<td></td>
</tr>
</tbody>
</table>
Management after adrenalectomy:

- **Confirmation of biochemical cure:**
  - aldosterone is measured the morning after the surgery to confirm a biochemical cure

- **Medications:**
  - Mineralocorticoid receptor antagonists and potassium supplements are discontinued
  - Number and dosages of antihypertensive medications are usually cut by 50%
  - Any medications that may contribute to hyperkalemia (such as ACE inhibitors and ARBs) are usually discontinued

- **Patient counseling/expectation:**
  - Hypertension related to PA improves in 1–3 months after surgery (not immediately)
  - Risk of postoperative hypokalemia
  - Kidney dysfunction
Post-adrenalectomy management: risk of hyperkalemia

• Retrospective study, Mayo Clinic Rochester
• 2004-2015
• Inclusion criteria: AVS with lateralization, adrenalectomy, post-adrenalectomy biochemical data
• 192 patients
  – Hyperkalemia (>5.2 mmol/L): 12 (6.3%)
  – Median K of 5.5 (5.2-6.2 mmol/L)
  – Median 13.5 days (7-55)
  – Treatment of hyperkalemia:
    • No treatment in 5 patients (duration of hyperkalemia median 17 days)
    • Fludrocortisone (4 patients)
    • Sodium Polysterene sulfonate (1 patient) and chlorthalidone (1 patient)
  – Contralateral suppression index cutoff 0.47
• Management: potassium levels weekly for 4 weeks after surgery

Shariq 2018
Post-adrenalectomy management: risk of hyperkalemia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Highest postoperative K, mmol/L</th>
<th>Time to onset of hyperK, d</th>
<th>Management</th>
<th>Duration of hyperkalemia, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.3</td>
<td>14</td>
<td>Resolved spontaneously</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>5.5</td>
<td>13</td>
<td>Resolved spontaneously</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>5.8</td>
<td>7</td>
<td>Fludrocortisone 0.15 mg/d</td>
<td>262</td>
</tr>
<tr>
<td>4</td>
<td>5.2</td>
<td>14</td>
<td>Fludrocortisone 0.05 – 0.1 mg/d</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>5.4</td>
<td>7</td>
<td>Resolved spontaneously</td>
<td>121</td>
</tr>
<tr>
<td>6</td>
<td>6.1</td>
<td>55</td>
<td>Hydrocortisone 15 mg/d</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>5.3</td>
<td>7</td>
<td>Resolved spontaneously</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>5.4</td>
<td>15</td>
<td>Chlorthalidone 12.5 mg/d</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>5.4</td>
<td>7</td>
<td>Fludrocortisone 0.5 mg/d</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>6.2</td>
<td>18</td>
<td>Sodium polystyrene sulfonate</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>5.8</td>
<td>18</td>
<td>Resolved spontaneously</td>
<td>18</td>
</tr>
<tr>
<td>12</td>
<td>5.6</td>
<td>13</td>
<td>Limited dietary K</td>
<td>42*</td>
</tr>
</tbody>
</table>
Renal function after surgery 
(unmasking of kidney dysfunction)

• Most patients with long-standing PA have some degree of renal insufficiency that is masked by the glomerular hyperfiltration associated with aldosterone excess

• Circa 40% of patients with PA show a clinically important decrease in renal function after surgery → average decrease in GFR is around 20%
What is success of treatment in patients with PA?

- Retrospective study, Mayo Clinic Rochester
- 1993-2011
- Inclusion criteria: AVS with lateralization, unilateral adrenalectomy, follow up data
- Post-adrenalectomy
  - Hypertension was cured in 42%
  - Hypertension improved in 47%
  - No improvement/worsening in 12%
  - Hypokalemia improved in 97%, unknown in 3%
What is success of treatment in patients with PA?

• **International consortium:** 1994-2015
• 705 patients with unilateral PA (AVS) undergoing adrenalectomy, 699 with biochemical data
• 6-12 months follow up:
  – Complete clinical success in 37%
  – Partial clinical success in 47%
  – Complete biochemical success in 94%
• Women, younger patients and lower levels of preoperative medications predicted clinical success
Clinical success

Brisbane (n=45)
Torino (n=80)
Paris (n=62)
Yokohama City (n=76)
Kyoto (n=40)
Berlin (n=45)
Ljubljana (n=44)
Rochester (n=83)
Sendai (n=63)
Nijmegen (n=38)
Warsaw (n=30)
Munich (n=99)

Absent success  Complete success  Partial success  Range of outcome
Biochemical success
Medical therapy

• Mineralocorticoid receptor antagonists (MRA)
  – **Spironolactone**
    • Nonselective MRA
    • Starting dose 25 daily → titrate to achieve high normal potassium. Usual effective dose of 100-300 mg daily
    • Concomitant therapy with salicylates should be avoided as they decrease the effectiveness of spironolactone
    • Side effects: gynecomastia, erectile dysfunction and decreased libido in men, menstrual irregularity in women
    • Monitor Blood pressure, potassium and creatinine weekly
  – **Eplerenone**
    • Competitive selective MRA (<1% binding affinity to androgen and progesterone receptors)
    • Starting dose 25 BID → titrate to achieve high normal potassium
    • Usual effective dose is 200-300 mg daily
    • Monitor BP, K, creatinine weekly

• Second agents: usually diuretics – hydrochlorothiazide
Is medical therapy for primary aldosteronism effective?

- Longitudinal study assessing efficacy of medical management of PA
- 602 pts with PA (treated with MRAs) matched with 41,853 pts with essential hypertension—both with comparable CV risk profiles and BP control
- PA group: CV events ↑ 2-fold, ↑ risk of mortality (1.34), diabetes (1.26), and atrial fibrillation (1.93)
  - risks were limited to the PA subgroup where PRA remained <1 ng/mL/hr (suggesting subtherapeutic dosages of MRAs)
- Surgically treated patients with PA had 0.58 risk of CV events compared with essential hypertension

Hundemer, et al, Lancet Diab Endo 2018
Is medical therapy for primary aldosteronism effective?

 противопоказания для антигипертензивного лечения

 First study comparing quality of life in patients with PA treated with surgery versus medical management

 92 pts treated with MRAs and with 92 pts treated with adrenalectomy: QoL assessed at baseline, 6, and 12 months: RAND SF-36 & EQ-5D

 At baseline, QoL scores were lower in patients with PA compared with the general population, especially in women

 After 12 months:

  Adrenalectomy: almost all QoL measures had normalized

  MRA therapy: most QoL measures had improved but not all to the level of the general population.

 Velema et al. JCEM 2019
TAKE AWAY POINTS:

- Case detection testing: anyone with hypertension
- Medications may cause false negatives but not false positives: no need to stop medications if renin is suppressed
- Confirmatory testing is not needed in everyone
- Most medically treated patients are on suboptimal dosages of MRAs → remain at increased CV risk
- Surgery is superior to medical therapy in reversing low QoL scores in patients with PA
- Risk of hyperkalemia after surgery may be predicted by CSI

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