How do I investigate suspected secondary hypertension?

Marie Freel
RCP Update in Medicine
23rd November 2016
World beaters.....!
Hypertension often poorly controlled

Prevalance of hypertension categories, by age and sex
Base: Aged 16 and over with three valid BP measurements

Scottish Health Survey 2009
Hypertension targets just got lower......

SPRINT investigators NEJM 2015 373:2103-2116
Secondary hypertension

- 5-10% of ‘essential’ hypertension cases
- Clinical ‘clues’ important
- Age based approach essential
## Secondary hypertension according to age

<table>
<thead>
<tr>
<th>Age group</th>
<th>% with underlying cause</th>
<th>Most common cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (&lt;12 years)</td>
<td>70-85%</td>
<td>Renal parenchymal disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coarctation of aorta</td>
</tr>
<tr>
<td>Adolescents (12-18 years)</td>
<td>10-15%</td>
<td>Renal parenchymal disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coarctation of aorta</td>
</tr>
<tr>
<td>Young adults (19-39 years)</td>
<td>5%</td>
<td>Fibromuscular dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal parenchymal disease</td>
</tr>
<tr>
<td>Middle aged adults (40-65 years)</td>
<td>8-12%</td>
<td>Primary Aldosteronism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obstructive Sleep Apnoea</td>
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<tr>
<td></td>
<td></td>
<td>Cushing’s syndrome</td>
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<tr>
<td></td>
<td></td>
<td>Phaeochromocytoma</td>
</tr>
<tr>
<td>Older adults</td>
<td>17%</td>
<td>Atherosclerotic renovascular disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal failure hypothyroidism</td>
</tr>
</tbody>
</table>
Secondary hypertension

- 5-10% of ‘essential’ hypertension cases
- Clinical ‘clues’ important
- Age based approach essential
- Consider if:
  - Severe or resistant hypertension
  - Child/adolescent
  - Worsening of previously stable hypertension
  - Malignant hypertension
  - No other risk factors identified and age <30
Secondary hypertension: investigations

- Renal function and urinalysis
- Renal imaging
  - Ultrasound
  - MRA renal arteries
- Aldosterone to renin ratio (ARR)
- 24h urine for catecholamines/metanephrines
  - Only if clinical suspicion
Case 1: Just another case of hypertension……?

- 32 y female
- 3 years of hypertension, well controlled on ramipril
- But now BP difficult to control (162/95 mm/Hg) despite addition of amlodipine
- UE: Na 136, K 4.1 Cl 95 Ur 4.2 Cr 68
- Plasma aldosterone (supine) 420 pmol/L (100-400), plasma renin activity (PRC) 1.2 µIU/ml (5-44.9)
  - Aldosterone to renin ratio (ARR) 350
The myths of Primary Aldosteronism (PA)?

- PA is a rare cause of hypertension
- Serum potassium must be normal
- All the drugs must be stopped!
- Making the diagnosis doesn’t matter - just lower the blood pressure!
A Prospective Study of the Prevalence of Primary Aldosteronism in 1,125 Hypertensive Patients

Gian Paolo Rossi, MD, FACC, FAHA, Giampaolo Bernini, MD, Chiara Caliumi, MD, Giovambattista Desideri, MD, Bruno Fabris, MD, Claudio Ferri, MD, Chiara Ganzaroli, MD, Gilberta Giacchetti, MD, Claudio Letizia, MD, Mauro Maccario, MD, Francesca Mallamaci, MD, Massimo Mannelli, MD, Mee-Jung Mattarello, MD, Angelica Moretti, MD, Gaetana Palumbo, MD, Gabriele Parenti, MD, Enzo Porteri, MD, Andrea Semplicini, MD, FAHA, Damiano Rizzoni, MD, Ermanno Rossi, MD, Marco Boscaro, MD, Achille Cesare Pessina, MD, PhD, Franco Mantero, MD, for the PAPY Study Investigators

Padova, Ancona, Reggio Emilia, Pisa, L’Aquila, Palermo, Legnano, Roma, Firenze, Torino, and Reggio Calabria, Italy

Frequency of aldosteronism in hypertension:

4.8% Aldosterone Producing Adenoma
6.4% Idiopathic Hyperaldosteronism
The myths of Primary Aldosteronism (PA)?

- PA is a rare cause of hypertension
- Serum potassium must be normal
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Hypokalaemia and Primary Aldosteronism

Rossi et al. J Am Coll Cardiol 2006
The myths of Primary Aldosteronism (PA)?

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on aldosterone</th>
<th>Effect on renin</th>
<th>Effect on ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-blocker</td>
<td>↓</td>
<td>↓↓</td>
<td>↑</td>
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<tr>
<td>Centrally acting</td>
<td>↓</td>
<td>↓↓</td>
<td>↑</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>↓</td>
<td>↓↓</td>
<td>↑</td>
</tr>
<tr>
<td>K-wasting diuretics</td>
<td>↔↑</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>K-sparing diuretics</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>↓</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Ca channel blockers (DHP)</td>
<td>↔↓</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
The myths of Primary Aldosteronism (PA)?

- PA is a rare cause of hypertension
- Serum potassium must be normal
- All drugs must be stopped
- Making the diagnosis doesn’t matter—just lower the blood pressure!
Lower the blood pressure stupid.

(Gordon McInnes)
Increased cardiovascular morbidity in Primary Aldosteronism

Milliez et al, JACC 2005, 45, 1243-8

- CVA: OR 4.2 (2-8.6)
- MI: OR 6.5 (1.5-27.4)
- AF: OR 1.6 (1-2.5)
- Echo LVH: OR 12.1 (3.2-45.2)
- ECG LVH: OR 2.9 (1.8-4.6)
### Table 3. Published Series on Primary Aldosteronism and Cardiovascular Complications

<table>
<thead>
<tr>
<th>Published Series</th>
<th>Number of patients</th>
<th>Blood Pressure</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Takeda et al⁵⁷</td>
<td>224 patients with</td>
<td>170±26/94±15</td>
<td>Myocardial infarction (1.8% vs 4.0%) Heart failure (3.6% vs 4.0%)</td>
</tr>
<tr>
<td></td>
<td>surgically proven APA</td>
<td>179±25/106±17</td>
<td></td>
</tr>
<tr>
<td>Milliez et al⁴</td>
<td>124 patients with PA</td>
<td>176±23/107±14</td>
<td>Myocardial infarction (4.0% vs 0.6%; OR, 6.5) Atrial fibrillation (7.3% vs 0.6%; OR, 12.1)</td>
</tr>
<tr>
<td>Catena et al⁷⁷</td>
<td>54 patients with PA</td>
<td>167±16/103±9</td>
<td>Cardiovascular events more frequent in PA patients (35% vs 11%; OR, 4.61; P&lt;0.001) Sustained arrhythmia (15% vs 3%; OR, 4.93) Cerebrovascular events (11% vs 3%; OR, 4.36) Coronary heart disease (20% vs 8%; OR, 2.80)</td>
</tr>
<tr>
<td>Current study</td>
<td>459 patients with PA</td>
<td>151±24/88±13</td>
<td>Myocardial infarction (4.4% vs 1.7%; OR, 2.8) Atrial fibrillation (3.9% vs 1.1%; OR, 4.3) Coronary artery disease (5.7% vs 2.8%; OR, 2.2) Heart failure (4.1% vs 1.2%; OR, 3.5)</td>
</tr>
</tbody>
</table>

Savard et al Hypertension 2013
Diagnosis of PA

The Management of Primary Aldosteronism:
Case Detection, Diagnosis, and Treatment:
An Endocrine Society Clinical Practice Guideline

John W. Funder, Robert M. Carey, Franco Mantero, M. Hassan Murad, Martin Reincke, Hirotaka Shibata, Michael Stowasser, and William F. Young, Jr

Hudson Institute of Medical Research (J.W.F.), Clayton, VIC 3168, Australia; University of Virginia Health System (R.M.C.), Charlottesville, Virginia 22908; University of Padova (F.M.), 35122 Padua, Italy; Mayo Clinic, Evidence-based Practice Center (M.H.M.), Rochester, Minnesota 55905; Klinikum of the Ludwig-Maximilians-University of Munich (M.R.), 80366 München, Bavaria, Germany; Oita University (H.S.), Oita 870-1124, Japan; University of Queensland (M.S.), Brisbane, Australia; and Mayo Clinic (W.F.Y.), Rochester, Minnesota 55905

J Clin Endocrinol Metab 2016
Diagnosis of PA: a guideline based approach

Patients with Hypertension that are at Increased Risk for PA

- PA Unlikely
  - ARR to Detect Cases (1|□□□□)
    - +
      - Patient Unwilling/Unable to Proceed
      - ↓K⁺, renin, PAC >20 ng/dL
    - -
  - Confirmatory Testing (1|□□□□)
    - +
      - No Need for Confirmatory Testing (2|□□□□)
      - Treat with MR Antagonist (2|□□□□)
    - -
  - Adrenal CT (1|□□□□)
    - +
      - If Surgery Desired
        - AVS (1|□□□□)
          - Bilateral
            - Treat with MR Antagonist (1|□□□□)
          - Unilateral
            - Marked PA, Young Age, and + CT (2|□□□□)
              - Treat with Laparoscopic Adrenalectomy (1|□□□□)
        - If Surgery Not Desired
          - Subtype Testing

- PA Unlikely
  - +
    - Patient Unwilling/Unable to Proceed
  - -

Diagnosis of PA: a guideline based approach

Patients with Hypertension that are at Increased Risk for PA

PA Unlikely

ARR to Detect Cases (1[⊕⊕⊙⊙])

Aldosterone 420 pmol/L
PRC 1.2 μIU/ml
ARR =350; > 35 merits investigation
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PRC 1.2 µIU/ml
ARR = 350; > 35 merits investigation

Saline suppression test
2 litres saline/4 hours:
Baseline: PRC 1.1/aldo 410
4 hours: PRC < 0.5/aldo 305
Diagnosis of PA: a guideline based approach

Patients with Hypertension that are at Increased Risk for PA

- PA Unlikely
  - ARR to Detect Cases (1|⊕⊕ΟΟ)
  - Confirmatory Testing (1|⊕⊕ΟΟ)
  - Adrenal CT (1|⊕⊕ΟΟ)

Aldosterone 420 pmol/L
PRC 1.2 μIU/ml
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Saline suppression test
2 litres saline/4 hours:
Baseline: PRC 1.1/aldo 410
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Diagnosis of PA: a guideline based approach

Aldosterone 395 pmol/L
PRC 1.2 µIU/ml
ARR =329; > 35 merits investigation

Saline suppression test
2 litres saline/4 hours:
Baseline: PRC 1.1/aldo 410
4 hours: PRC<0.5/aldo 305
PA subtype classification- adenoma v hyperplasia

- CT has insufficient sensitivity and specificity
- Adrenal vein sampling (AVS) can confirm unilateral aldosterone excess
- Recommended in all patients >40 years or in younger patients with no visible adenoma on CT
- Only performed if surgery indicated
Adrenal Vein Sampling (AVS)

- Technical issues: right adrenal problematic
  - 74% success for right adrenal (384 patients)
  - 97% success rate in Mayo clinic (Rossi JCEM 2001)

- Lack of operator experience is main determinant of outcome
Alternatives to AVS

• Clinical prediction of aldosterone producing adrenal adenoma:
  – Size ~ 1cm
  – K < 3.5 mmol/l
  – eGFR > 100

(Kupers et al, JCEM 2012)

• $^{11}$C-Metomidate PET CT
PA: outcome after surgery

- BP improves in almost all, serum [K] normalises in 100%
- Long-term cure rates of hypertension 30-60%
- Persistent hypertension more likely if:
  - 2 or more anti-hypertensive agents
  - Older age
  - ↑ serum creatinine
  - Longer duration of hypertension
- So, need to manage expectations
Case 1 outcome:

- Left adrenalectomy
- 3 months later:
  - BP 128/82 mm/Hg on amlodipine only
  - PRC now 14 µIU/ml
  - Plasma aldosterone: 285 pmol/L
Case 2: To stent or not to stent?

- 28 year old female, referred to MAU with ‘hypertension’ and ‘headache’
- OCP recently stopped due to BP (ABPM 164/108 mm/Hg)
- PMH: pyelonephritis
- No FH
- O/E:
  - Lean. BP 195/130 mm/Hg, pulse 92.
  - CV exam normal, femoral pulses palpable
  - Fundoscopy: bilateral flame haemorrhages, no papilloedema
  - Urinalysis: +++ protein; UE: eGFR normal, [K] 3.2
Malignant (accelerated) hypertension

- Severe hypertension with **bilateral retinal haemorrhages and exudates** +/- papilloedema
- No absolute blood pressure level (usually > 180/120 mm/Hg) to confirm or exclude diagnosis
- Always merits investigation for secondary cause
  - Renal artery stenosis cause of up to 45% cases of malignant hypertension
Case 2: continued

- Plasma renin concentration: 211 µIU/ml (5-44.9)
- Plasma aldosterone: 507 pmol/L (100-400)
- US renal tract:
  - The right kidney measures 9.6 cm and the left kidney 10.7 cm in length. Both kidneys appear normal with no focal abnormality or hydronephrosis visualised.
- Next investigation??
Renal MR angiogram
Renal fibromuscular dysplasia (FMD)

• Non-inflammatory non-atherosclerotic disorder causing renal artery stenosis
• Unusual, <1% of cases of hypertension
• Can involve other arteries
  – Mesenteric arteries most commonly
• Bilateral in 35-50%
Clinical features - renovascular hypertension

- Hypertension
- Activation of RAAS
- Clinical suspicion:
  - Severe/resistant hypertension (esp >55y)
  - Hypertension <35y
  - Sudden rise in BP
  - Significant increase in creatinine after ACEi/ARB without drop in BP
  - Widespread atheroma or asymmetrical kidneys
Management of FMD

• Control blood pressure:
  – ACEi usually ok (watch Cr); only contraindicated in severe bilateral disease
  – But young woman of child-bearing age…….

• Stenting of renal artery
  – Usually percutaneous
  – Hypertension cure rates 20-80%
  – Stabilises renal function
Left renal artery stenosis confirmed
BP improved with ACEi and thiazide diuretic
Underwent PTA of renal artery May 2016
BP now 125/69 on no treatment
Renal artery stenting in atherosclerotic renovascular disease

- 3 large, randomised clinical trials since 2009
  - ASTRAL n=806; > 40% stenosis
    • (NEJM 2009 361:1953-1962)
  - STAR n=140; >40% stenosis
    • (Ann Int Med 2009 150:840-848)
  - CORAL n=947; >60% stenosis
    • (NEJM 370:13-22)

- All show NO BENEFIT in renal artery stenting compared to medical therapy in atheromatous reno-vascular disease
Case 3: spells, sweating and flushing

- 39 year old man, ex-professional rugby player
- Presented with chest pain and hypertension
- Previous ‘episodes’
  - During exercise: ‘grey’ ‘sweaty and clammy’, headache, vomiting
- On arrival:
  - BP 190/110, ST elevation, positive troponin, pulmonary oedema
- Treatment:
  - IV metoprolol: BP rose to 230/150
Case 3:

- Coronary angiogram: normal coronary arteries
- CT abdomen:
Case 3:

U Catecholamine Mets View Cumulative Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Ref. Range (Units)</th>
<th>Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h U Van‘lic Acid.</td>
<td>* 665</td>
<td>&lt;35 umol/24h (umol/24h)</td>
<td>+</td>
</tr>
<tr>
<td>24h U 5HIAA</td>
<td>38</td>
<td>&lt;50 umol/24h (umol/24h)</td>
<td></td>
</tr>
<tr>
<td>24h U H’vanillic Ac</td>
<td>* 42</td>
<td>&lt;40 umol/24h (umol/24h)</td>
<td>+</td>
</tr>
<tr>
<td>24h U Noradrenaline</td>
<td>* 43094</td>
<td>&lt;900 nmol/24h (nmol/24h)</td>
<td>+</td>
</tr>
<tr>
<td>24h U Adrenaline</td>
<td>* 42822</td>
<td>&lt;230 nmol/24h (nmol/24h)</td>
<td>+</td>
</tr>
<tr>
<td>24h U Dopamine</td>
<td>* 4229</td>
<td>&lt;3300 nmol/24h (nmol/24h)</td>
<td>+</td>
</tr>
<tr>
<td>24h U Fr Normet‘ine</td>
<td>* 8584</td>
<td>&lt;650 nmol/24h (nmol/24h)</td>
<td>+</td>
</tr>
<tr>
<td>24h U Fr Metad‘ine</td>
<td>* 12368</td>
<td>&lt;350 nmol/24h (nmol/24h)</td>
<td>+</td>
</tr>
</tbody>
</table>

* Abnormal    ** Not in use

Analysis performed at Biochemistry Dept, Crosshouse Hospital
Results phoned to M Freil.
bb262767y
Phaeochromocytoma

- Accounts for <0.2% of patients with hypertension

- Indications for screening:
  - Headache, sweating and tachycardia
  - ‘spells’ with palpitations, headache, pallor
  - Genetic predisposition
  - Adrenal adenoma
Phaeochromocytoma-screening

- 24h urine fractionated metanephrines
  - 98% sensitivity/specificity
- Plasma metanephrines
  - From cannula, supine, fasting
  - Very sensitive, less specific (77-85%)
  - Reserve for cases with high clinical suspicion
Phaeochromocytoma: false positive results

- Any acute illness, esp CV/MI/CCF/OSA
- **Tricyclic anti-depressants**
- Decongestant cold remedies
- Amphetamines/cocaine
- Buspirone and most psychoactive agents
- Prochlorperazine
- Ethanol
Imaging in phaeochromocytoma

- CT or MRI both very sensitive but 70% specificity due to ‘incidentalomas’
  - Heterogeneous, vascular, cystic, dense adrenal lesions
- No concern about use of IV contrast if not alpha-blocked

- Diagnostic $^{123}$I-MIBG if:
  - Large phaeo (>10 cm)
  - Paraganglioma
Phaeochromocytoma: imaging characteristics
Imaging in phaeochromocytoma

- CT or MRI both very sensitive but 70% specificity due to ‘incidentalomas’
  - Heterogeneous, vascular, cystic, dense adrenal lesions
- No concern about use of IV contrast if not alpha-blocked

- Diagnostic $^{123}$I-MIBG if:
  - Large phaeo (>10 cm)
  - Paraganglioma
Phaeochromocytoma-key points

• It is not common
• Beware of interfering medications
• Pallor and headache are good discriminating symptoms
• If symptoms present, diagnosis should be straightforward
Case 3 outcome

- Phenoxybenzamine 80 mg bd, labetolol 200 mg tds
- Laparoscopic adrenalectomy
- Currently normotensive, normal LV systolic function
- Genetic screen negative
Summary

• Majority of hypertension is ‘primary’
• Consider screening if:
  – Young
  – Malignant hypertension
  – Resistant hypertension
  – Newly uncontrolled hypertension
• Main screening tests:
  – ARR (beware but don’t be put off by drugs)
  – 24h urinary metanephrines
  – Renal ultrasound
  – Renal doppler or MRA renal arteries