When to suspect & how to detect endocrine hypertension

Mark Gurnell

Wellcome Trust-MRC Institute of Metabolic Science
<table>
<thead>
<tr>
<th><strong>Secondary hypertension – when to suspect</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe hypertension:</strong></td>
</tr>
<tr>
<td>- Systolic ≥180 mmHg &amp;/or diastolic ≥110 mmHg</td>
</tr>
<tr>
<td><strong>Resistant hypertension:</strong></td>
</tr>
<tr>
<td>- uncontrolled on 3 or more agents</td>
</tr>
<tr>
<td><strong>Acute rise or increased lability of BP</strong></td>
</tr>
<tr>
<td>- in previously stable patient</td>
</tr>
<tr>
<td><strong>Malignant / accelerated hypertension:</strong></td>
</tr>
<tr>
<td>- with end organ damage</td>
</tr>
<tr>
<td><strong>Age of onset &lt;30 years:</strong></td>
</tr>
<tr>
<td>- esp. in non-obese subject with no family history</td>
</tr>
<tr>
<td><strong>Hypertension with electrolyte abnormality:</strong></td>
</tr>
<tr>
<td>- esp. hypokalaemic alkalosis</td>
</tr>
<tr>
<td><strong>Hypertension in a patient with an adrenal incidentaloma</strong></td>
</tr>
</tbody>
</table>
Secondary hypertension – aetiology

- **Renal** (e.g. renovascular or chronic renal disease)
- **Endocrine**
  - Primary (hyper)aldosteronism (Conn syndrome)
  - Other states of mineralocorticoid excess:
    - excessive liquorice ingestion
    - congenital adrenal hyperplasia (CAH)
    - deoxycorticosterone (DOC)-secreting adrenal tumour
    - Liddle syndrome; syndrome of apparent mineralocorticoid excess
  - Phaeochromocytoma / paraganglioma (PPGL)
  - Cushing syndrome
  - Acromegaly
  - Hyperparathyroidism
  - Thyroid disease (hypo- or hyper-thyroidism)
- **Metabolic** (diabetes/metabolic syndrome, obesity)
- **Pregnancy**
- **Medications** (COCP, NSAIDs, corticosteroids, stimulants etc)
- **Other** (coarctation, sleep apnoea syndrome)
Case 1 – presentation

A 36-yr-old previously fit man is admitted with sudden onset occipital headache, slurred speech and dizziness.

His pulse is 70 bpm regular and blood pressure 235/145 mmHg. The remainder of the cardiovascular, respiratory and abdominal examinations are normal.

Neurological assessment reveals dysarthria, dysmetria and ataxia with a broad-based gait.

**Fundoscopy:**
Case 1 – initial investigations

Laboratory:

<table>
<thead>
<tr>
<th>Haematology</th>
<th>Value</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>165</td>
<td>130–170 g/L</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.51</td>
<td>0.4–0.54</td>
</tr>
<tr>
<td>MCV</td>
<td>90</td>
<td>80–96 f/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>350</td>
<td>150–450 x10⁹/L</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Biochemistry</th>
<th>Value</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium</td>
<td>141</td>
<td>135–145 mmol/L</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>3.5</td>
<td>3.4–5.0 mmol/L</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>90</td>
<td>60–110 µmol/L</td>
</tr>
</tbody>
</table>

Renal doppler ultrasound: unremarkable

MRI Head
Question 1

Which is the most likely endocrine cause of severe / malignant phase hypertension in this patient?

A  Acromegaly
B  Cushing syndrome
C  Diabetes mellitus
D  Phaeochromocytoma
E  Primary aldosteronism

Correct answer:   E
Primary aldosteronism (PA)
Background: adrenal physiology & anatomy

Angiotensin II → ZG → Aldosterone

ACTH → ZF → Cortisol

ACTH → ZR → Androgens

Splanchnic nerves → Medulla → Noradrenaline/Adrenaline

The renin-angiotensin-aldosterone system

Case 1 – further investigation

Investigations:

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<tr>
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</tr>
<tr>
<td>Serum creatinine</td>
<td>90</td>
<td>60–110 μmol/L</td>
</tr>
<tr>
<td>Plasma renin concentration</td>
<td>4.0</td>
<td>5.4–60 mU/L</td>
</tr>
<tr>
<td>Plasma aldosterone concentration</td>
<td>657</td>
<td>135–400 pmol/L</td>
</tr>
<tr>
<td>Aldosterone:renin ratio (ARR)</td>
<td>164</td>
<td>&lt;84</td>
</tr>
</tbody>
</table>

Investigations:

- CT adrenals
- $^{11}$C-metomidate PET/CT
- Left adrenal
Primary aldosteronism

The legacy…

‘Conn syndrome is a rare condition, occurring in <1% of all patients with hypertension.’

Kumar & Clark, 2008

NICE Hypertension Update, 2011

NHS Choices, 2011
Primary aldosteronism

The reality…

The commonest curable secondary cause of hypertension, present in approximately:

• 5–10% of unselected patients with hypertension

• 20–25% of those with resistant hypertension

(If 25% of UK adult population have hypertension, then up to 1 million with PA)

Primary aldosteronism

The hope…

Potentially curative surgery/intervention could be offered in up to 50% of PA patients,

• normalising serum potassium
• improving hypertension (with reduced drug burden)
• ameliorating effects of hyperaldosteronism
PA - response to adrenalectomy (n=34)

Pre-operative BP

Systolic BP (mm Hg)

Diastolic BP (mm Hg)

mean = 147/89

Number of anti-hypertensives

Number of patients

mean = 2.56

Post-operative BP

Systolic BP (mm Hg)

Diastolic BP (mm Hg)

mean = 136/84

Number of anti-hypertensives

Number of patients

mean = 1.29
PA – potential limitations of medical therapy

Primary aldosteronism – multiple challenges...

The hurdles...

‘Successful’ surgery…?
Lateralisation
Confirmatory testing
Renin, aldosterone screening
Consider diagnosis

Case 2 – presentation and initial investigations

A 63-yr-old man has persistent hypertension despite treatment with indapamide, amlodipine and ramipril. He had a myocardial infarction three years ago, for which he is taking atenolol, clopidogrel and simvastatin.

His pulse is 64 bpm regular and blood pressure 168/95 mmHg. The remainder of the physical examination is unremarkable.

Investigations:

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<th>Value</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium</td>
<td>134</td>
<td>135–145 mmol/L</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>3.1</td>
<td>3.4–5.0 mmol/L</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>90</td>
<td>60–110 μmol/L</td>
</tr>
<tr>
<td>Plasma renin concentration</td>
<td>&lt;2.0</td>
<td>5.4–60 mU/L</td>
</tr>
<tr>
<td>Plasma aldosterone concentration</td>
<td>395</td>
<td>135–400 pmol/L</td>
</tr>
</tbody>
</table>
Question 2a

Which is the next most appropriate step in management?

A  Adrenal vein sampling

B  Confirmatory testing (e.g. hypertonic saline infusion test)

C  CT scan of adrenals

D  MR scan of adrenals

E  Repeat baseline biochemistry

Correct answer: E
Question 2b

Which medication should be prioritised for temporary discontinuation before repeating measurement of renin and aldosterone?

A  Amlodipine
B  Atenolol
C  Clopidogrel
D  Indapamide
E  Ramipril

Correct answer:  B
<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect on laboratory results</th>
<th>Minimum drug washout period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td>↑↑ renin ↑ aldosterone</td>
<td>↓ ARR FALSE NEGATIVE</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
<td></td>
<td>2 weeks</td>
</tr>
<tr>
<td><strong>Beta blockers</strong></td>
<td>↓↓ renin ↓ aldosterone</td>
<td>↑ ARR FALSE POSITIVE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 weeks</td>
</tr>
<tr>
<td><strong>K⁺ losing diuretics</strong></td>
<td>↑↑ renin ↔ or ↑ aldosterone</td>
<td>↓ ARR FALSE NEGATIVE</td>
</tr>
<tr>
<td>(e.g. furosemide, bendroflumethiazide)</td>
<td></td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>K⁺ sparing diuretics</strong></td>
<td>↑↑ renin ↑ aldosterone</td>
<td>↓ ARR FALSE NEGATIVE</td>
</tr>
<tr>
<td>(e.g. spironolactone, eplerenone, amiloride)</td>
<td></td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>Dihydropyridine CCBs</strong></td>
<td>↔ or ↑ renin ↔ or ↑ aldosterone</td>
<td>↓ ARR FALSE NEGATIVE</td>
</tr>
<tr>
<td>(e.g. amlodipine, felodipine)</td>
<td></td>
<td>2 weeks</td>
</tr>
<tr>
<td><strong>Non-dihydropyridine CCBs</strong></td>
<td>No significant effect</td>
<td>No significant effect</td>
</tr>
<tr>
<td>(e.g. verapamil, diltiazem)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>α₁ adrenoceptor antagonists</strong></td>
<td>No significant effect</td>
<td>No significant effect</td>
</tr>
<tr>
<td>(e.g. doxazosin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vasodilators</strong></td>
<td>No significant effect</td>
<td>No significant effect</td>
</tr>
<tr>
<td>(e.g. hydralazine)</td>
<td></td>
<td></td>
</tr>
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# Antihypertensive medications & screening for PA

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<th>Medication</th>
<th>Effect on laboratory results</th>
<th>Minimum drug washout period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low dietary sodium intake</strong></td>
<td>↑↑ renin ↓ aldosterone</td>
<td>↓ ARR FALSE NEGATIVE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 weeks</td>
</tr>
<tr>
<td><strong>High dietary sodium intake</strong></td>
<td>↓↓ renin ↓ aldosterone</td>
<td>↑ ARR FALSE POSITIVE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 weeks</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>↑↑ renin ↔ or ↑ aldosterone</td>
<td>↓ ARR FALSE NEGATIVE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 weeks</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>↑↑ renin ↑ aldosterone</td>
<td>↓ ARR FALSE NEGATIVE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td>↔ or ↑ renin ↔ or ↓ aldosterone</td>
<td>↓ ARR FALSE NEGATIVE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 weeks</td>
</tr>
<tr>
<td>No significant effect</td>
<td>No significant effect</td>
<td>Not required</td>
</tr>
<tr>
<td>No significant effect</td>
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<td>No significant effect</td>
<td>No significant effect</td>
<td>Not required</td>
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</table>
Question 2c

Which advice is most appropriate when drawing blood to determine the aldosterone:renin ratio (ARR)?

A  Advise abstinence from alcohol consumption for a minimum of 2 weeks prior to sampling

B  Limit dietary sodium intake for 48 h prior to venepuncture

C  Perform venepuncture after the patient has been seated for 10 min

D  Transfer samples urgently to the laboratory on ice

E  Where possible, collect blood when the patient is hypokalaemic

Correct answer: C
A 29-yr-old woman with type 1 diabetes, treated with a continuous subcutaneous insulin infusion, reports increasing difficulty in controlling her blood glucose levels. She has longstanding microvascular complications (retinopathy and microalbuminuria). Her other medications include ramipril and the combined oral contraceptive pill.

Her pulse is 66 bpm regular and blood pressure 173/95 mmHg. Her body mass index is 28.5 kg/m². She has mild bilateral pitting oedema of both ankles.
Case 3 – initial investigations

Laboratory:

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<td>3.2</td>
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</tr>
<tr>
<td>Serum creatinine</td>
<td>84</td>
<td>60–110 µmol/L</td>
</tr>
<tr>
<td>HbA1c</td>
<td>68</td>
<td>30–42 mmol/mol</td>
</tr>
</tbody>
</table>
Question 3a

Which is the most likely cause for her deteriorating glycaemic control?

A Coexistent autoimmune hypothyroidism
B Coexistent adrenal insufficiency
C Development of insulin resistance
D Diminishing endogenous insulin production
E Poor adherence to dietary modification

Correct answer: C
Question 3b

Which investigation is most appropriate as an initial screening test for hypercortisolism?

A  24 h urinary free cortisol (UFC)
B  Late night salivary cortisol (LNSC)
C  Overnight dexamethasone suppression test (DST)
D  Plasma adrenocorticotrophic hormone (ACTH)
E  Sleeping midnight serum cortisol

Correct answer: A or B
Cushing syndrome – a multisystem disorder requiring multimodal therapy

What is the probability that the patient has Cushing’s syndrome?

Clinical assessment

- Truncal obesity - 96%
- Facial plethora - 82%
- Diabetes/IGT - 80%
- Gonadal dysfunction - 74%
- Hirsutism/acne - 72%
- Hypertension - 68%
- Proximal myopathy - 64%
- Bruising/striae - 62%
- Mood disorders - 58%
- Osteoporosis - 38%
- Oedema - 18%
- Polydipsia/polyuria - 10%
- Fungal infections - 6%

Low
Intermediate
High
Cushing’s syndrome – diagnosis

What is the probability that the patient has Cushing’s syndrome?

Low

Intermediate

High

Clinical assessment

Sign/Symptom | % frequency in Cushing’s
--- | ---
Truncal obesity | 96
Facial plethora | 82
Diabetes/IGT | 80
Gonadal dysfunction | 74
Hirsutism/acne | 72
Hypertension | 68
Proximal myopathy | 64
Bruising/striae | 62
Mood disorders | 58
Osteoporosis | 38
Oedema | 18
Polydipsia/polyuria | 10
Fungal infections | 6

Single test (care!)

≥ 2 tests (± repeats)
Cushing’s syndrome – dexamethasone testing

<table>
<thead>
<tr>
<th>False POSITIVE dexamethasone suppression testing</th>
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<tbody>
<tr>
<td>Pseudo-Cushing’s syndrome</td>
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<td>Non-concordance</td>
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<tr>
<td>Oral E2 therapy</td>
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<td>Enzyme-inducing agents</td>
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<td>Fast metabolizer</td>
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<table>
<thead>
<tr>
<th>False NEGATIVE dexamethasone suppression testing</th>
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</thead>
<tbody>
<tr>
<td>Cushing’s syndrome (slow metabolizers)</td>
</tr>
<tr>
<td>Cyclical Cushing’s syndrome</td>
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</table>
False positive DST

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Variable performance of 24h UFC & LNSC in CS

Twenty-four-hour urine free cortisol (UFC) & LNSC in 11 patients with surgically proven Cushing's syndrome

Potential limitations of LNSC in diabetes

Case 4 – presentation

A 51-yr-old man has a 6 month history of intermittent sweating episodes and headaches. He was diagnosed with hypertension two years ago and reports a longstanding history of anxiety and low mood. His current medications are ramipril, amlodipine and amitriptyline.

His pulse is 76 bpm regular and blood pressure 150/85 mmHg sitting and 135/80 mmHg standing for 2 min. His body mass index is 29.5 kg/m². There are no other abnormal findings on examination.
Laboratory:

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<tbody>
<tr>
<td>Plasma metanephrine</td>
<td>348</td>
<td>&lt;600 pmol/L</td>
</tr>
<tr>
<td>Plasma normetanephrine</td>
<td>1455</td>
<td>&lt;1000 pmol/L</td>
</tr>
</tbody>
</table>

CT C/A/P: unremarkable

$^{123}$I-MIBG scan:
Question 4a

Which is the most appropriate next investigation?

A $^{18}$F-FDG PET scan
B $^{68}$Ga-Dotatate PET scan
C MR scan of the head & neck
D No further imaging indicated
E Ultrasound scan of the bladder

Correct answer: D
Case 4 – repeat investigations 4 weeks later

Laboratory:

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<tr>
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<th>Value</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Plasma metanephrine</td>
<td>323</td>
<td>&lt;600 pmol/L</td>
</tr>
<tr>
<td>Plasma normetanephrine</td>
<td>768</td>
<td>&lt;1000 pmol/L</td>
</tr>
</tbody>
</table>
Which is the most likely explanation for the normalisation of the plasma normetanephrine result?

A. $^{131}$I-MIBG therapy
B. Commencement of CPAP for obstructive sleep apnoea
C. Left adrenalectomy
D. Medication change
E. Sample measurement in another laboratory

Correct answer: D
PPGL – clinical features

• hypertension
  - persistent or paroxysmal
  - labile BP
• hypotension (esp. postural)
• palpitations / arrhythmias
• headaches
• sweating (generalised); pallor (not flushing)
• tremor
• marked / unexplained anxiety (episodic)
• syndromic (increasing proportion can now be shown to have a genetic basis)
Potential causes of false positive PPGL screen

- medications
  - tricyclic antidepressants
  - sympathomimetics
  - antihypertensives (e.g. $\alpha$-adrenoceptor antagonists)
  - paracetamol (assay dependent)
- primary (essential) hypertension
- obstructive sleep apnoea (OSA)
- physiological stress
- acute intercurrent illness / surgery
- sampling issues
Acromegaly – a multisystem disorder requiring multimodal therapy

Secondary hypertension – endocrine causes

• Renal (renovascular disease; chronic renal disease)

• Endocrine
  • Primary (hyper)aldosteronism (Conn syndrome)
  • Other states of mineralocorticoid excess:
    - excessive liquorice ingestion
    - congenital adrenal hyperplasia (CAH)
    - deoxycorticosterone (DOC)-secreting adrenal tumour
    - Liddle syndrome; syndrome of apparent mineralocorticoid excess
  • Phaeochromocytoma / paraganglioma (PPGL)
  • Cushing syndrome
  • Acromegaly
  • Hyperparathyroidism
  • Thyroid disease (hypo- or hyper-thyroidism)

• Metabolic (diabetes/metabolic syndrome, obesity)

• Pregnancy

• Medications (COC, NSAIDs, corticosteroids, stimulants etc)

• Other (coarctation, sleep apnoea syndrome)
Summary: screening for endocrine hypertension

- **Primary aldosteronism**
  - **Screening:** plasma renin and aldosterone [→ ARR (aldosterone:renin ratio)]
  - **Confirmation:** saline suppression / oral salt loading

- **Phaeochromocytoma/paraganglioma**
  - Plasma or urinary metanephrines (± 3 methoxytyramine)

- **Cushing syndrome**
  - Dexamethasone suppression / UFC / late night salivary cortisol

- **Acromegaly**
  - GH suppression during OGTT, IGF-1

- **Thyroid / parathyroid disease**
  - Free thyroxine and TSH; corrected calcium & PTH
Questions?