Adrenals, steroids and blood pressure
Marie Frei
CoMEP Teaching Session: Endocrinology
28th March 2014

Lecture plan
• Adrenal insufficiency
• Need for intravenous steroids in critically ill patients
• BHS/NICE guideline for diagnosis and management of essential hypertension
• Clinical features and screening for adrenal causes of hypertension

Adrenal glands - a reminder
• Adrenal cortex:
  – Mineralocorticoids (aldosterone)
  – Glucocorticoids (cortisol)
  – Androgens (androstenedione/DHEA)
• Adrenal medulla:
  – Catecholamines

Adrenal insufficiency
• Primary
  – Addison’s, CAH
  – Life threatening
• Secondary
  – Pituitary/hypothalamic disease
  – Minter disease
  – No need for mineralocorticoid replacement
• Iatrogenic
  – Commonest cause!

Case
• 23 year old woman
• 6 months of lethargy, weight loss and amenorrhoea
• Referred with intractable vomiting, abdominal pain and dehydration
• On arrival:
  – BP 85/55 mmHg, pulse 110 bpm
  – Pigmented
  – Na 125 K 7.1 Urea 12 Cr 135
Adrenal insufficiency

- If suspect—— TREAT
- Glucocorticoid replacement
  - IV hydrocortisone 100 mg qds, then 50 mg qds
- Mineralocorticoid replacement
  - Not required if on high dose glucocorticoid
  - Start once one < 30 mg daily of hydrocortisone

Diagnosis of adrenal insufficiency in non acute setting

- 4 stages in development of primary adrenal insufficiency:
  - Stage 1: High plasma renin activity and normal or low serum aldosterone
  - Stage 2: Impaired serum cortisol response to ACTH stimulation
  - Stage 3: Increased morning plasma ACTH with normal serum cortisol
  - Stage 4: Low morning serum cortisol and overt clinical adrenal insufficiency

Diagnosis of adrenal insufficiency in acute setting

- Treat first, diagnose later
- Random cortisol (retrospective) on arrival
  - Prior to hydrocortisone
- Formal short synacthen test once haemodynamically stable:
  - Do not need to stop hydrocortisone
  - Withhold night and early morning dose
  - Post ACTH cortisol < 480 nmol/L diagnostic
  - Prednisolone cross reacts with cortisol assay

Diagnosis of adrenal insufficiency in non acute setting

- Short synacthen test:
  - Most sensitive in morning, but will be abnormal at any time of day if clinically obvious adrenal insufficiency
  - Misleading in recent onset ACTH deficiency (secondary hypoadrenalism)
  - Not required if early am cortisol > 300nmol/L
- Measure ACTH
- Plasma renin and aldosterone
  - Renin increased, aldosterone undetectable
- Anti-adrenal antibodies
  - Negative in > 10% of Addison’s cases

Chronic management of adrenal insufficiency

- Switch to oral steroid replacement once stable:
  - Hydrocortisone preferred
  - Initially supraphysiological, eventually 20 mg daily in divided doses
  - Try to follow circadian rhythm
- Mineralocorticoid replacement
  - Fludrocortisone once < 30 mg hydrocortisone
  - Monitor BP and serum K

Management of chronic adrenal insufficiency in hospital

- Minor illness
  - Double up oral steroid for 3 days
- Major illness
  - Parenteral glucocorticoid
- Nausea and vomiting
  - Parenteral glucocorticoid, if vomiting <2h after last steroid dose
- Surgery
  - Depends on severity of operation
  - Minor procedures give 100 mg IV hydrocortisone prior to procedure (eg. OGD)
  - Major procedures 100 mg IV tds for at least 3 days then taper
Steroid dependency identification

- Always carry this card with you and show it to medical staff when taking steroids. A regular dose of hydrocortisone is required in an emergency. (Steroid treatment card: http://www.rcplondon.ac.uk/doctor-development/your-practice/plan-care/develop-steroid-treatment-card-sick-day-rules)

- I atrogenic adrenal suppression: generally obvious, may not be clinically apparent in low doses. Commonest cause of adrenal insufficiency: in the UK, oral steroid for malignancy, inflammatory disease, stressful illness, and various topical preparations. Commonest cause of adrenal insufficiency: in the UK, oral steroid for malignancy, inflammatory disease, stressful illness, and various topical preparations.

- Iatrogenic adrenal suppression: high risk regimens: > 20mg pred/day for > 3 weeks, Cushingoid appearance. Low risk regimens: < 3 week course, < 5mg/day, alternate day therapy. Intermediate risk: 10-20mg/day > 3 weeks.

Steroid dose comparisons

<table>
<thead>
<tr>
<th>Name</th>
<th>Equivalent dose in milligrams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Adrenal insufficiency

- Primary
  - Addison’s, CAH
  - Life threatening
- Secondary
  - Pituitary/hypothalamic disease
  - Milder disease
  - No need for mineralocorticoid replacement
- Iatrogenic

Implications of ‘iatrogenic’ adrenal insufficiency

- May not look Cushingoid
- Need to apply ‘sick day’ rules
  - Increase dose during intercurrent illness
- DO NOT STOP STEROIDS SUDDENLY
Glucocorticoid dose tapering (prednisolone)

- Aim for rate of change to prevent disease recurrence and symptoms of cortisol deficiency
- **60mg**: 10 mg/day every 1-2 weeks
- **20-60 mg**: 5 mg/day every 1-2 weeks
- **10-19 mg**: 2.5mg/day every 1-2 weeks
- **5-9 mg**: 1mg/day every 1-2 weeks
- **<5 mg**: 0.5 mg/day every 1-2 weeks (if required) **OR**
  - Switch to hydrocortisone treatment

Steroid replacement in critically ill patients

The impact of acute illness on HPA axis

- *Relative* adrenal insufficiency
  - Suboptimal cortisol production during septic shock/critical illness
  - Controversial and no consensus as to diagnostic criteria
  - Has led to questions as to whether parenteral steroid required during severe illness especially when associated with hypotension

Surviving sepsis guideline for use of steroids in shock

3. Corticosteroids
   1. Not using intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for initial Resuscitation). In case this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C).
   2. Not using the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone (grade 2B).
   3. In treated patients hydrocortisone tapered when vasopressors are no longer required (grade 2D).
   4. Corticosteroids not be administered for the treatment of sepsis in the absence of shock (grade 1D).
   5. When hydrocortisone is given, use continuous flow (grade 2D).
Overall recommendations

- Laboratory assays of plasma cortisol concentration and response to adrenocorticotropic hormone (ACTH) stimulation are likely unreliable in critically ill patients.
- In patients without shock, or patients with less severe septic shock corticosteroid therapy does not appear to be beneficial.
- Intravenous corticosteroid therapy (200 to 300 mg per day) should be administered to adult patients with severe septic shock (SBP<90 mmHg for >1 hour despite adequate fluid resuscitation/vasopressor administration).
- Response to ACTH testing should not be used to select patients for corticosteroid therapy.
- Administer IV hydrocortisone for 5-7 days and then taper dose.

Endocrine Hypertension

Prevalence of hypertension

Scottish Health survey 2003

Hypertension prevalence worldwide

Key changes in BHS/NICE Hypertension guideline

- Diagnosis
  - Use of ABPM HBPM encouraged
- Initiating and modifying treatment
  - Anyone with stage 2 hypertension
  - Stage 1 if CV risk sufficient
  - Benefit in treating >80y
- Choice of anti-hypertensive therapy
  - ‘thiazide like’ diuretic at stage 3

Requirements for interpretation of ABPM HBPM

- ABPM:
  - at least two measurements per hour during the person’s usual waking hours
  - average of at least 14 measurements to confirm diagnosis
- HBPM:
  - Two consecutive seated measurements, at least 1 minute apart
  - Blood pressure is recorded twice a day for at least 4 days and preferably for a week
  - Measurements on the first day are discarded (average value of all remaining is used)
Stage 2 hypertension
- CBPM ≥160/100 mmHg & ABPM/HBPM ≥ 150/95 mmHg
- If target organ damage present or 10-year cardiovascular risk > 20%
- If younger than 40 years or black of African or Caribbean family origin of any age
- Aged under 55 years or black person
- If target organ damage present or 10-year cardiovascular risk > 20%

Offer antihypertensive drug treatment
Offer patient education and interventions to support adherence to treatment
Offer annual review of care to monitor blood pressure, provide support and discuss lifestyle, symptoms and medication

Stage 1 hypertension
- CBPM ≥140/90 mmHg & ABPM/HBPM ≥ 135/85 mmHg
- If younger than 40 years or black of African or Caribbean family origin of any age
- Aged under 55 years or black person
- If target organ damage present or 10-year cardiovascular risk > 20%

Offer lifestyle interventions

Resistant hypertension
- A + C + D + consider further diuretic or alpha- or beta-blocker
- Consider seeking expert advice

Case
- 54y woman
- Hypertension for many years
- Stopped medications 9 months ago
- Presents with ‘headache’
  - BP 220/130 mm/Hg
  - Fundoscopy: retinal haemorrhages/exudates, no papilloedema
- Management ?

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
- Hypertensive encephalopathy
  - Signs of cerebral oedema
  - Insidious onset of headache/nausea/vomiting
  - Need to exclude CVA

Management of malignant hypertension
- Medical emergency
- Lower the BP
  - Parenteral medications better as rapidly reversed if significant hypotension
  - eg. Labetalol/GTN/hydralazine/nitroprusside
- Goal of treatment
  - Aim to lower DBP to 100-105 mm/Hg over a few hours
  - Switch to oral treatment once BP controlled and stable
- Investigate for secondary causes

When to consider secondary hypertension?
- Young age
- Resistant hypertension
- Severe hypertension at presentation
- Obvious phenotype
Adrenal causes of secondary hypertension

- Primary Aldosteronism
- Phaeochromocytoma
- Cortisol excess

Primary Aldosteronism

- Commonest ‘secondary’ cause of hypertension
  - Prevalence approximately 11%
    - 40% adenoma; 60% bilateral hyperplasia
- Hypokalaemia present in less than 50% of cases
- Aldosterone-renin-ratio (ARR) best screening tool
  - > 35 should prompt further investigation

Effect of anti-hypertensives on the ARR

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect on aldosterone levels</th>
<th>Effect on renin levels</th>
<th>Effect on ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-adrenergic blockers</td>
<td>↓</td>
<td>↓</td>
<td>↑ (EP)</td>
</tr>
<tr>
<td>Central alpha-2 agonists (e.g., clonidine, alphavasodilators)</td>
<td>↓</td>
<td>↓</td>
<td>↑ (EP)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>↓</td>
<td>↓</td>
<td>↑ (EP)</td>
</tr>
<tr>
<td>K⁺-wasting diuretics</td>
<td>↓</td>
<td>↑</td>
<td>↓ (EN)</td>
</tr>
<tr>
<td>K⁺-sparking diuretics</td>
<td>↑</td>
<td>↑</td>
<td>↓ (EN)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>↓</td>
<td>↑</td>
<td>↓ (EN)</td>
</tr>
<tr>
<td>ARBs</td>
<td>↓</td>
<td>↑</td>
<td>↓ (EN)</td>
</tr>
<tr>
<td>Ca²⁺ blockers (DHPa)</td>
<td>↓</td>
<td>↑</td>
<td>↓ (EP)</td>
</tr>
<tr>
<td>Renin inhibitors</td>
<td>↓</td>
<td>↑</td>
<td>↓ (EP)</td>
</tr>
</tbody>
</table>

Management of PA

- Medical treatment just as effective as surgical treatment in reversing end organ damage
- Surgical cure rate 20-60%
- Mineralocorticoid receptor antagonists
  - Spironolactone: limited by anti-androgen side effects
  - Eplerenone: pure MR antagonist, but less potent
- Block mineralocorticoid effects (target sodium channel in renal distal tubule)
  - Amiloride in high dose

Phaeochromocytoma

- Rare; 0.05-0.2% of hypertension cases
- Can be asymptomatic (up to 50%)
- Hypertension
  - Can be episodic
  - Postural hypotension
- Other features: headache, pallor, abdominal pain, tachycardia
- Screening:
  - 24h urine for catecholamines and fractionated metanephrines
  - 98% sensitivity and specificity

Cushing’s syndrome

- Hypertension and obesity common, but cortisol excess found in 1% of patients with hypertension
- Clinical suspicion important
  - Striae
  - Easy bruising/thin skin
  - Proximal myopathy
- Screening tests:
  - 24h UFC
  - Overnight dexamethasone suppression test
Summary

• Do not wait for diagnosis before treating adrenal insufficiency
• Be aware of how to manage steroid dependent patients in a hospital setting
• Adrenal function difficult to assess in severe illness
• Intravenous hydrocortisone may be beneficial in critically ill patients with refractory shock
• Endocrine hypertension rare, except for Primary Aldosteronism