A case of confirmed primary hyperaldosteronism diagnosed despite normal screening investigations

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Mr B (63m) presented with resistant hypertension, diagnosed aged 46, associated with significant hypokalaemia over the past four years. He remained hypertensive (150/90mmHg) despite controlled release metoprolol 47.5mg, felodipine 10mg, losartan 25mg, terazosin 5mg and spironolactone 25mg (all once daily). Serum potassium concentration was 3.9mmol/L (normal range 3.5–5.3) on four tablets of potassium daily (10 tablets per day before spironolactone). After withdrawing spironolactone for six weeks, the plasma aldosterone concentration was 283pmol/L with a plasma renin activity of 0.7nmol/L/hour, giving an Aldosterone Renin ratio (ARR) of 441(normal <750). Other endocrine causes of hypertension were excluded.

An abdominal CT scan excluded reno-vascular causes of hypertension and demonstrated a likely adenomatous 9x12mm left adrenal nodule (Figure 1). On the basis of a significant pre-test probability of hyperaldosteronism (clinical presentation and adrenal nodule), we proceeded to a saline infusion test (SIT) having first withdrawn spironolactone (six weeks), Losartan (four weeks) and metoprolol (two weeks). This test demonstrated an abnormal baseline ARR, but apparent normal aldosterone suppression at four hours (Table 1).

Table 1: Results from a saline infusion test (SIT).

<table>
<thead>
<tr>
<th></th>
<th>Plasma aldosterone (pmol/l)</th>
<th>Plasma renin (mIU/L)</th>
<th>Serum potassium (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saline infusion test A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 0</td>
<td>585</td>
<td>39.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Time +240</td>
<td>124</td>
<td>16.7</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>Saline infusion test B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 0</td>
<td>575</td>
<td>28.8</td>
<td>3.7</td>
</tr>
<tr>
<td>Time +240</td>
<td>392</td>
<td>-</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Aldosterone, renin and potassium concentrations were measured immediately before and after the infusion of 2,000ml of 0.9% saline over four hours while the patient remained seated. 40mmol of potassium was added to the infusion during SIT B. An aldosterone concentration of <140 pmol/L at 4 hours represents normal suppression, while a level >210 pmol/L confirms hyperaldosteronism.

ABSTRACT

Primary hyperaldosteronism is a common cause of hypertension in the adult population. We report a case of histologically and biochemically confirmed hyperaldosteronism related to an adrenal adenoma, where initial screening and biochemical tests were potentially misleading. The case highlights the importance of clinical suspicion in the current diagnostic approach to primary hyperaldosteronism.
As hypokalaemia had developed during the SIT, this was repeated with potassium added to the saline infusion. On this occasion, post-infusion aldosterone concentrations were clearly inappropriately elevated, confirming a biochemical diagnosis of hyperaldosteronism (Table 1). Mr B proceeded to adrenal vein sampling (AVS), which confirmed lateralisation of hyperaldosteronism to the left adrenal gland, consistent with the radiological findings (Figure 1).

Following stabilisation of blood pressure and potassium concentrations, Mr B underwent left posterior retroperitoneoscopic adrenalectomy without complication. Histological analysis confirmed an adrenocortical adenoma with nodular proliferations of adrenocortical tissue elsewhere in the specimen. At follow up, Mr B has a serum potassium of 4.7mmol/L (no supplements) and a blood pressure of 130/78mmHg on daily Metoprolol 47.5mg and Felodipine 10mg.

Summary

This case illustrates some complexities in the screening for and diagnosis of a common cause of hypertension. Hyperaldosteronism is identified in approximately 6% of cases of adult hypertension, with case detection on the basis of clinical features recommended by recent guidelines (see Figure 2). In contrast to historical opinion, hypokalaemia is now known to be present in only a minority of patients with hyperaldosteronism, with normokalaemic hypertension representing the typical presentation. Confirmation of hyperaldosteronism is of value as it provides the opportunity for resection of unilateral adrenal pathology with resultant resolution of hypokalaemia, and significant improvements in blood pressure control and cardiovascular morbidity independent of the degree of hypertension.

In this confirmed case of hyperaldosteronism, it is of interest to consider the initial diagnostic tests. The screening test was normal, dissuading the attending physician of the need to further explore the possibility of hyperaldosteronism. To increase the ease of testing for a common condition, guidelines recommend screening for hyperaldosteronism while the patient is on anti-hypertensive medications bar spironolactone, epleronone and potassium wasting diuretics. However, the concurrent use of interfering medications or dietary sodium restriction may significantly decrease the sensitivity of the ARR for detecting hyperaldosteronism, unless an altered diagnostic cut-off is utilised. Thus, a normal screening ARR does not exclude hyperaldosteronism and the result should be interpreted in light of the clinical probability of hyperaldosteronism. Here, a repeat ARR under more stringent test conditions was clearly abnormal.

Hypokalaemia is a potent inhibitor of aldosterone release in health, and potentially also in the context of hyperaldosteronism, falsely lowering the circulating aldosterone concentrations. During the first SIT, potassium concentrations fell significantly, which may have directly lowered the circulating aldosterone concentration. With potassium added to the saline infusion during the second study, normokalaemia was maintained and circulating aldosterone concentrations were clearly inappropriately elevated.

Hyperaldosteronism is a common cause of hypertension. In the context of screening for or confirming biochemical hyperaldosteronism, normal results should not
necessarily be considered definitive, especially if current medication use is likely to affect the sensitivity of the ARR, or significant hypokalaemia is present. If the clinical picture is suggestive, it may be reasonable to either repeat testing or occasionally pursue a diagnosis of primary hyperaldosteronism despite initial normal tests, after discussion with an endocrinologist.

**Figure 2:** Endocrine society guidelines for the case detection of primary hyperaldosteronism.²

- Blood pressure >150/100mmHg on each of three measurements on different days
- Blood pressure (140/90mmHg) resistant to three conventional anti-hypertensive drugs, or controlled on ≥4 drugs
- Hypertension and spontaneous or diuretic induced hypokalaemia
- Hypertension and an adrenal incidentaloma
- Hypertension and sleep apnoea
- Hypertension and a family history of early onset hypertension or a stroke at <40 years of age
- Hypertensive first-degree relatives of patients with primary hyperaldosteronism
Competing interests:
Nil.

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