Persistent Hypokalaemia in a Jamaican Hypertensive Patient
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ABSTRACT

We report the case of a 48-year old man with uncontrolled hypertension and persistent hypokalaemia from an aldosterone producing adrenal adenoma treated by laparoscopic adrenalectomy. Clinicians’ identification of primary hyperaldosteronism is critical as the correct treatment results in improved blood pressure control and reduced risk of complications.

Keywords: Caribbean, diagnosis, hyperaldosteronism, primary, therapy

INTRODUCTION

Primary aldosteronism (PA) is a group of disorders in which aldosterone production is inappropriately high, autonomous of the renin-angiotensin system and not suppressed by sodium loading (1). Bilateral idiopathic hyperaldosteronism (IHA) and aldosterone producing adenoma (APA) are the most common subtypes of PA. It is estimated that more than 10% of hypertensive patients in both general and specialty settings are a result of PA (2, 3). Additionally, 10 to 20 per cent of patients with resistant hypertension are found to have PA (4). Confirming the diagnosis is particularly important as patients with PA have higher cardiovascular morbidity and mortality than age/sex matched controls with essential hypertension for the same degree of blood pressure elevation (5). Elevated aldosterone in PA increases the risk of myocardial infarction, stroke, left ventricular hypertrophy and atrial fibrillation through its effect on blood pressure as well as by inducing vascular and perivascular inflammation in the heart, brain and kidney (6). In this paper, we report a case of PA describing the diagnostic evaluation, therapeutic options, clinical management and potential improvement in outcomes with well-treated disease.

CASE REPORT

A 48-year old Caribbean male was referred for evaluation of chest pain. He had a one-year history of difficult to control hypertension, despite therapy with fosinopril 20 mg daily, hydrochlorothiazide 25 mg daily and amlodipine 5 mg daily. He had no family history of hypertension and denied any previous use of corticosteroids, non-steroidal anti-inflammatory drugs, laxatives or herbal supplements. He was a non-smoker and did not consume alcohol. On examination he was a healthy looking male, BMI of 27 kg/m² with a seated blood pressure in the left arm of 140/90 mm Hg. There was no thyromegaly, radio-femoral delay, cardiomegaly, abdominal masses or bruit and no hypertensive retinopathy. His initial laboratory evaluation revealed hypokalaemia of 3.2 mmol/L, normal BUN, creatinine, lipid...
profile and normal thyroid function. An echocardiogram and exercise nuclear cardiac stress test (Thallium) were normal. The fosinopril and hydrochlorothiazide were replaced by perindopril (Indapamide 4 mg/0.625 mg) and four subsequent laboratory tests revealed persistent hypokalaemia (all less than 3.5 mmol/L) over the next twelve months. Aldactone was commenced and he was referred for evaluation for possible hyperaldosteronism.

In preparation for his initial screening test for PA, aldactone and perindopril/indapamide were discontinued and the patient was placed on extended release nifedipine and potassium supplements. Plasma renin and aldosterone were collected after normalization of his serum potassium. Plasma renin (angiotensin I generation and liquid chromatography tandem mass spectrometry, Quest Diagnostics) was 0.5 ng/ml/hr (reference value > 0.65), plasma aldosterone (liquid chromatography tandem mass spectrometry, Quest Diagnostics) was 74 ng/dL (reference value 4–31) with an aldosterone renin ratio (ARR) of 156 (reference value < 30). A plasma aldosterone of 11 ng/dL after infusion of 2 litres normal saline over 4 hours confirmed the diagnosis of PA. A computed tomography (CT) of the adrenal glands revealed a 1.1 cm size adrenal adenoma in the left adrenal gland (Figure), however, he elected to be treated medically. Aldactone was resumed and the dose titrated until his blood pressure was controlled and his potassium normalized. Eighteen months after commencing aldactone he developed painful gynaecomastia. Aldactone was again discontinued and the patient referred to the National Institutes of Health for adrenal vein sampling (AVS). On AVS, there was suppression of aldosterone production from the right adrenal gland, consistent with the presence of a left-sided aldosterone-producing adrenal adenoma (Table). He reversed his previous decision and accepted laparoscopic surgical removal of the adenoma; the patient’s hypertension improved and the potassium levels returned to normal without the use of potassium supplements. He was discharged post surgery on 60 mg of extended release nifedipine and this was subsequently reduced to 30 mg once daily. The gynaecomastia resolved and at his most recent visit he continued to have excellent blood pressure control and normal serum potassium.

### DISCUSSION

The presence of late onset hypertension, persistent hypokalaemia or difficult to control hypertension should raise the clinician’s suspicion of PA as a cause of secondary hypertension. Primary aldosteronism is the most common secondary cause of hypertension associated with hypokalaemia in middle aged adults (40–64 years).

The aldosterone renin ratio is the recommended initial screening test for PA (1). The measurement of both aldosterone and renin is superior to measurement of aldosterone or renin in isolation (1, 7). Serum potassium should not be used for screening as only 9–37% of patients would have low levels (8). Antihypertensive medications that might interfere with ARR results should be discontinued. Diuretics, ACEIs, ARBs, β-blockers and clonidine are stopped two weeks prior to testing while aldosterone antagonists (spironolactone or eplerenone) should be discontinued at least four weeks prior to testing (1). Calcium channel blockers (preferably from the

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**Table:** Results of bilateral adrenal venous sampling for the patient. The ratio of adrenal vein cortisol to peripheral vein more than 10:1 indicates successful catheterization of the relevant veins. The lateralization ratio of 128:1 is consistent with a left adrenal adenoma.

<table>
<thead>
<tr>
<th>Vein</th>
<th>Aldosterone (A) ng/dL</th>
<th>Cortisol (C) µg/dL</th>
<th>A:C ratio ratio*</th>
<th>Aldosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left adrenal vein</td>
<td>11 000</td>
<td>238</td>
<td>46.21</td>
<td>128:1</td>
</tr>
<tr>
<td>Right adrenal vein</td>
<td>190</td>
<td>514</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Peripheral vein</td>
<td>65</td>
<td>15.2</td>
<td>4.27</td>
<td></td>
</tr>
</tbody>
</table>

*Left adrenal A:C ratio divided by right adrenal vein A:C ratio

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**Figure:** Multi detector computed tomography (MDCT) of the adrenal glands showing 1.1 cm size adenoma (arrow) in the left adrenal gland.
non-dihydropyridine group), hydralazine, and peripheral alpha-blockers are recommended for blood pressure control during this period. Hypokalaemia inhibits aldosterone secretion and must be corrected before the ARR is obtained. Aldosterone and renin levels should be measured in the morning at least two hours after waking and in the upright/sitting position. Primary aldosteronism is suspected if the morning ARR is > 20–40 (plasma renin expressed as ng/mL per hour) and the plasma aldosterone > 15 ng/dL (1). Attention to the plasma aldosterone concentration is important as an elevated ARR ratio can also be obtained in patients with low-renin hypertension. The initial studies in our patient met these criteria.

It is generally recommended that all patients with a positive ARR undergo confirmatory testing, regardless of the ARR value, to prevent costly and intrusive lateralization procedures being performed in individuals with false-positive results (1). Confirmatory procedures include oral sodium loading, saline infusion, fludrocortisone suppression, and captopril challenge. There is insufficient evidence to recommend one over the others (1) so the choice of confirmatory test is determined by cost, patient health and compliance, laboratory resources and local expertise.

Salt suppression tests are the most commonly used (1, 9). The salt loading tests rely on the body’s physiological response to increased sodium. In patients with PA, saline infusion does not suppress aldosterone production. The saline suppression test used in our patient involves intravenous administration of 2 litres of normal saline over four hours with the blood taken for aldosterone immediately after the infusion is completed. If the post saline infusion plasma aldosterone levels are > 10 ng/dL, PA is likely and it is unlikely if the levels are < 5 ng/dL. Aldosterone levels between 5 and 10 ng/dL are considered indeterminate (1).

Distinguishing between unilateral and bilateral disease is important because unilateral adrenalectomy in patients with APA results in resolution of hypokalaemia and normalization of blood pressure (30–60%) or improvement in blood pressure (10, 11). In bilateral IHA, unilateral or bilateral adrenalectomy seldom corrects the hypertension (12), and so medical therapy is the treatment of choice. Biochemical tests to differentiate APA from IHA, such as 18 hydroxycorticosterone or changes in aldosterone with standing, have been replaced by AVS. Adrenal vein sampling, not the CT scan, is the preferred test for differentiating APA from bilateral disease (13). The sensitivity and specificity of AVS (95 and 100%, respectively) for detecting unilateral aldosterone excess are superior to that of adrenal CT [78 and 75%, respectively] (14). The CT scan is primarily used to exclude large masses that may represent adrenal carcinoma and warrant removal based on malignant potential (1). Our patient elected not to have surgery initially and so localization studies were not performed.

Adrenal vein sampling involves catheterization of adrenal veins through a percutaneous femoral approach with simultaneous administration of cosyntropin. Cosyntropin administration increases the cortisol gradient between the adrenal vein and inferior vena cava (IVC) which helps to confirm the successful sampling of the adrenal vein. The procedure must be done by an experienced radiologist to improve the success rate and minimize the complications. Blood is obtained simultaneously from both adrenal veins and a peripheral vein, and assayed for aldosterone and cortisol concentrations. The adrenal/peripheral vein cortisol ratio more than 10:1 with the continuous cosyntropin infusion protocol (13) and more than 3:1 without the use of cosyntropin (15) indicate successful catheterization of the adrenal veins. With continuous cosyntropin administration, adrenal vein aldosterone concentrations must be divided by the respective cortisol concentrations to minimize the dilutional effects of inferior phrenic vein flow into the left adrenal vein and IVC flow into the right adrenal vein. A cortisol-corrected aldosterone ratio from high side to low side of more than 4:1 is used to indicate unilateral aldosterone excess; a ratio less than 3:1 is suggestive of bilateral aldosterone hypersecretion (13).

The index patient had laparoscopic unilateral adrenalectomy which is the recommended procedure for unilateral aldosterone hypersecretion (16). Compared with open adrenalectomy, laparoscopic adrenalectomy is associated with fewer complications and shorter hospital stay. Partial adrenalectomy is not recommended as it is associated with continuous elevation of aldosterone levels after the procedure (17). Surgical treatment for bilateral disease is not advocated as it is not associated with significant improvement in blood pressure control in most patients.

Treatment with mineralocorticoid receptor (MR) antagonists such as aldactone is recommended for patients with unilateral disease who cannot undergo surgery and those with bilateral adrenal disease (1). The index case was placed on medical therapy as he initially did not wish to have surgery performed. Spironolactone is the drug of choice and should be started with a low dose (12.5–25 mg once daily) and gradually titrated upward until blood pressure control is achieved. Higher doses and prolonged use are associated with side effects such as gynaecomastia, decreased libido and muscle cramps. Jeunemaitre et al reported an incidence of gynaecomastia of 6.9% with less than 50 mg spironolactone and 52% with more than 150 mg of spironolactone (18). Combined therapy with other antihypertensive medications is encouraged to avoid using high doses of spironolactone. Eplerenone, a newer MR antagonist that selectively binds to the MR, is associated with fewer endocrine side effects and is an alternative to spironolactone that could have been used in our patient, but was not available in Jamaica.

In summary, PA is a common cause of secondary hypertension that should be suspected in patients with resistant hypertension with or without hypokalaemia. Diagnostic evaluation for PA places a high value on preventing the morbidity and mortality associated with excess aldosterone.
production. Physicians need to be aware of PA and appropriately evaluate patients when this condition is suspected.

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REFERENCES