Role of imaging and adrenal venous sampling techniques in the diagnosis of primary aldosteronism.

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Abstract
Background: Primary aldosteronism (PA) is a rare condition characterized by inappropriately high secretion of aldosterone, independently of the renin-angiotensin system, not suppressed by sodium loading test. PA represents the most common cause of secondary hypertension and its early detection and treatment can help reduce the cardiovascular (CV) risk.

Case presentation: We report on a 42-year-old man who was referred to an outpatients’ clinic reporting headache and vomiting associated with hypertension and was discharged with oral antihypertensive medication (irbesartan) and low-sodium diet. Three years later, he underwent further hospitalization for muscle pain in lower limb associated with severe hypokalemia (1.7 mmol/L) and elevated creatine phosphokinase (CPK) levels (2634 U/L). Abdominal CT scan excluded the presence of adrenal lesions. Acute intravenous potassium chloride (KCL) supplementation normalized serum potassium level and the patient was discharged with diagnosis of rhabdomyolysis and hypokalemia and with antihypertensive medication (spironolactone: 100 mg/day and amlodipine: 5 mg/day) and oral KCL supplementation (600 mg/day). After pharmacological washout, an inappropriately high aldosterone concentration (75.10 pg/ml) and very low renin level (1.10 pg/ml) were detected. PA diagnosis was confirmed by oral saline infusion test (SIT). Aldosterone levels did not normalize after dexamethasone suppression testing. Abdominal MRI showed a nodule measuring 6 mm in the right adrenal. A subsequent adrenal venous sampling (AVS) confirmed the unilateral (right) lateralization of the aldosterone hypersecretion.

Conclusion: Although invasive, AVS is the gold standard test to differentiate PA subtypes in patients who can be considered ideal candidates for unilateral adrenalectomy.

Keywords: primary aldosteronism, secondary hypertension, hypokalemia, adrenal venous sampling, imaging techniques.

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Introduction

Primary aldosteronism (PA), also known as Conn’s syndrome (1), is a rare condition, which is estimated to affect up to 10% of the hypertensive population and up to 15-20% of the population with resistant hypertension (2). It is characterized by inappropriately elevated aldosterone secretion, relatively autonomous of the renin-angiotensin system, and not suppressed by sodium
loading test (3). PA is the most common form of secondary hypertension, while the protracted high excretion of potassium causes hypokalemia. The inappropriate production of aldosterone, if not detected early and treated, can increase cardiovascular (CV) risk leading to life-threatening consequences.

Unilateral aldosterone-producing adenoma (APA) and unilateral (UAH) or bilateral (BAH) adrenal hyperplasia are the most common causes of PA, while aldosterone-producing adrenocortical carcinoma, or inherited conditions of familial hyperaldosteronism, including glucocorticoid-remediable aldosteronism (GRA), are much rarer (3). Surgery is the most appropriate therapy for APA and UAH, while medical management is the treatment of choice for BAH, or for patients refusing surgery or who are not considered ideal candidates for adrenalectomy (4).

Adrenal imaging techniques (CT or MRI) are not able to detect all microadenomas and nodular hyperplasias and cannot always differentiate non-secreting incidentalomas from aldosterone-producing adenomas (5, 6). On the contrary, adrenal venous sampling (AVS) is considered the gold standard technique being the only one able to differentiate unilateral (APA/UAH) from bilateral (IHA) causes of PA (3, 5-7). For this reason, AVS is recommended in all patients with biochemical evidence of PA, despite it being considered a complex and potentially dangerous procedure (3, 5-7).

We report the case of a patient with PA in whom computed tomography (CT) of the abdomen, performed with contrast, had excluded the presence of adrenal lesions, while abdominal magnetic resonance imaging (MRI) revealed a 6 mm right adrenal gland nodule. The subsequent AVS confirmed the unilateral lateralization of the aldosterone excess.

Case presentation

A 42-year-old man was referred to the outpatients’ clinic reporting headache and vomiting associated with hypertension. For this, he was discharged with oral antihypertensive medication (irbesartan 150 mg once daily) and a low-sodium diet prescription. Three years later, he underwent a second hospitalization for muscle pain in the lower limb associated with severe hypokalemia (1.7 mmol/L), hypocalcemia (7.5 mg/dL) and elevated creatine phosphokinase (CPK) levels (2634 U/L). A CT scan of the abdomen performed with contrast excluded the presence of adrenal lesions. Acute intravenous potassium chloride (KCL) supplementation normalized serum potassium levels and the patient was discharged with a diagnosis of rhabdomyolysis and hypokalemia, and with an oral prescription of antihypertensive drugs (spironolactone 100 mg once daily plus amlodipine 5 mg once daily) and KCL supplementation (600 mg/day). After two weeks of pharmacological washout, an inappropriately high aldosterone concentration (75.10 pg/ml) and very low renin level
(1.10 pg/ml) were detected. The oral saline infusion test (SIT), performed with patient lying in a recumbent position during infusion of 2,000 mL of 0.9\% saline iv over 4 h, starting at 9.00 AM, confirmed the diagnosis of PA (Table 1).

Table 1 – Oral saline infusion test (SIT) was performed in our recumbent patient during infusion of 2,000 mL of 0.9\% saline iv over 4 h, starting at 9.00 A.M. Blood samples for aldosterone, renin, sodium, and plasma potassium were taken at time 0’ and after 4 h. Blood pressure and heart rate were monitored throughout the test.

<table>
<thead>
<tr>
<th></th>
<th>0’</th>
<th>240’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum aldosterone (pg/ml)</td>
<td>80.80</td>
<td>195.00</td>
</tr>
<tr>
<td>Plasma renin (pg/ml)</td>
<td>3.00</td>
<td>1.70</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>144</td>
<td>143</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.3</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Before proceeding with further instrumental assessment, a diagnosis of GRA was considered, but aldosterone levels did not normalize after the dexamethasone suppression test. In particular, supine plasma aldosterone and cortisol were measured after 4 days of dexamethasone (2.0 mg/day, orally). Blood samples were taken on the fifth day (aldosterone: 100 pg/ml; cortisol: 0.20 μg/dl). Abdominal MRI performed with a 1.5 Tesla unit (Philips Gyroscan S) without gadolinium-DTPA administration showed a nodule measuring 6 mm in the right adrenal (Figure 1). Subsequent adrenal venous sampling (AVS) confirmed the unilateral (right) lateralization of the aldosterone hypersecretion (Table 2). The patient refused the proposed of surgical treatment preferring an expectation management.

Table 2 - Adrenal venous sampling (AVS) of our patient showing the right lateralization of the aldosterone hypersecretion. AVS was performed using venous catheters introduced via both femoral veins in order to obtain the simultaneous catheterization of bilateral adrenal veins.

<table>
<thead>
<tr>
<th>Blood sampling sites</th>
<th>Serum aldosterone (pg/ml)</th>
<th>Serum cortisol (mcg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infrarenal inferior vena cava</td>
<td>277.00</td>
<td>17.59</td>
</tr>
<tr>
<td>Suprarenal inferior vena cava</td>
<td>226.00</td>
<td>18.47</td>
</tr>
<tr>
<td>Right adrenal vein</td>
<td>295.00</td>
<td>30.35</td>
</tr>
<tr>
<td>Left adrenal vein</td>
<td>109.00</td>
<td>15.79</td>
</tr>
</tbody>
</table>
Discussion.

In physiological conditions, aldosterone plays a key role in the control and maintenance of effective circulating blood volume, as well as normal sodium and potassium balance and blood pressure (BP) (8). Inappropriate secretion of aldosterone is characterized by a wide spectrum of severity, resulting in higher CV morbidity and mortality and an increased metabolic risk profile with potentially life-threatening consequences than in patients with essential hypertension and the same elevation level of BP. However, the assessment of plasma renin activity and hypertensive status can help to limit the field of potential aetiologies. PA is considered a rare finding, but it represents the most frequent cause of secondary hypertension, affecting up to 10% of the entire hypertensive population and up to 15-20% of those with resistant hypertension. In this condition, the inappropriately high production of aldosterone, relatively autonomous of the renin-angiotensin system, and not suppressible by the sodium loading test, causes plasma renin suppression, sodium retention and hypokalemia, the latter being caused by prolonged increase of potassium excretion. PA presentation is commonly characterized by normokalemic hypertension with hypokalemia reported in only a minority of cases with higher disease severity (9). Concerning our patient with severe hypertension, oral SIT confirmed the diagnosis of PA and hypokalemia was corrected by...
acute intravenous KCL supplementation. Two antihypertensive drugs were needed to obtain sufficient BP control. The most common cause of PA is represented by APA, or by BAH (micro- or macronodular), while UAH, aldosterone-producing adrenocortical carcinoma, aldosterone-producing ovarian tumour or inherited conditions of familial hyperaldosteronism, including glucocorticoid-remediable hyperaldosteronism, are rarer findings (3). In our case, aldosterone levels did not normalize after the dexamethasone suppression test, and diagnosis of GRA was excluded. However, dexamethasone suppression test has a low sensitivity and diagnosis can be confirmed or excluded only by genetic testing.

Adrenal CT scan is recommended as the first-line imaging technique for subtyping evaluation of PA to exclude larger masses (3, 10). In comparison with CT, MRI has no advantage in subtype evaluation, being more expensive and having less spatial resolution than CT (3). Concerning our case, the CT scan of the abdomen, performed with contrast, excluded the presence of adrenal lesions, while the MRI scan revealed a 6 mm right adrenal gland nodule. However, neither CT nor MRI can detect all microadenomas and nodular hyperplasias and cannot always differentiate non-secreting incidentalomas from aldosterone-producing adenomas (5, 6). In this context, although a complex and potentially dangerous procedure, AVS is considered the gold standard technique being the only one which can differentiate unilateral (APA/UAH) from bilateral (IHA) causes of PA (3, 5-7). For this reason, AVS is recommended in all patients with biochemical evidence of PA before proceeding with adrenalectomy (3, 5-7). In our patient, AVS confirmed the unilateral (right) lateralization of the aldosterone excess.

In conclusion, although invasive, AVS remains the method of choice for preoperative lateral localization only in patients with PA who can be considered ideal candidates for unilateral adrenalectomy and who do not refuse the surgical option.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

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