Primary Hyperaldosteronism Associated With Hypertensive Emergencies

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There is growing awareness of primary aldosteronism as a cause of secondary hypertension. Usually, it manifests as hypertension and hypokalemia, or as resistant hypertension. Much less often, primary aldosteronism may be detected after a hypertensive emergency has developed. We highlight this association by reporting on eight patients with a clinical diagnosis of primary aldosteronism whose course was complicated by a hypertensive crisis. In all patients, an elevated serum aldosterone was accompanied by a suppressed plasma renin activity despite the presence of a hypertensive crisis. A good outcome was obtained either with laparoscopic adrenalectomy (1 patient) or with an antihypertensive drug regimen that included an antialdosterone agent (7 patients). The differential diagnosis of hypertensive emergencies should include primary aldosteronism. Am J Hypertens 2006; 19:623–627 © 2006 American Journal of Hypertension, Ltd.

Jerome Conn, in 1955, first described primary aldosteronism (PA) as hypertension with hypokalemia due to an aldosterone-producing adrenal adenoma. Initial studies to look for this entity in hypertensive patients concluded that this form of hypertension was rare. Despite this early finding, it is now believed that PA may be as rare as initially thought. Although the exact reasons for this are unclear, it is likely that this is partly because hypertensive patients with normal serum potassium levels are being screened and tested and also due to the increased use of the aldosterone concentration (AC) to plasma renin activity (PRA) ratio (ARR) for screening.

In addition to the increased detection of PA, it also appears to have a broader clinical presentation than originally believed. Historically, the clinical presentation of PA is mild-to-moderate hypertension that may be resistant to treatment. More recently, PA has been associated with higher blood pressure (BP) elevations. The description of severe or emergent hypertension with acute target organ damage (hypertensive emergency) in PA has received less attention and the number of case reports to date is limited.

We describe eight clinical cases of PA (3 confirmed; 5 probable) associated with hypertensive emergencies seen by our Hypertension Consultation Service and illustrate some difficulties in pursuing definitive diagnostic testing is this subgroup with PA.

Methods

All eight patients were evaluated between 1993 and 2004 for acute hypertensive emergency. In all cases, other forms of secondary hypertension were excluded based on clinical and radiologic testing. A definite diagnosis of PA was made if urinary AC was >12 ng/dL and urinary sodium (Na+) >200 mEq/d. Probable PA was assumed if AC was >15 ng/dL and ARR was >40, but no diagnostic sodium suppression was performed or if results were indeterminate. Subtype determination was initially done with computerized tomography (CT) scan and adrenal vein sampling when possible. Adrenal vein sampling was typically done under cosyntropin stimulation according to the Dopman method. The adrenal venous aldosterone-to-cortisol ratio on the affected side had to be at least five times higher than on the contralateral side for the patient to be considered for surgery.

Laboratory reference ranges include potassium (K+) of 3.5 to 5.0 mEq/L and serum creatinine (Scr) of 0.6 to 1.2 mg/dL in all patients. Upright PRA ranges for all cases (1.0 to 9.0 ng/mL/h).

Cases

Case 1

D.L., a 52-year-old white man, has type 2 diabetes mellitus and poorly controlled hypertension since age 38 years despite treatment with 75 mg/d of captopril, 80 mg/d of...
furosemide, 800 mg/d of labetalol, and 40 mEq/d of potassium. He developed extreme BP elevation (280/170 mm Hg) with congestive cardiac failure. Pertinent physical findings included the presence of a fourth heart sound, diffuse pulmonary rales, and bilateral pitting leg edema. Initial testing showed moderate hypokalemia (2.9 mEq/L), SCr of 0.9 mg/dL, AC of 29 ng/dL, and PRA of 0.3 ng/mL/h. The electrocardiogram met criteria for left ventricular hypertrophy with strain pattern. Coronary and renal angiography demonstrated normal renal and coronary arteries with an ejection fraction of 30%. He did not have evidence of myocardial necrosis. Computed tomography of the adrenals revealed minor enlargement of the left gland. Salt suppression studies were not done due to the presence of heart failure. Treatment was changed to 100 mg of losartan, 80 mg of furosemide, nitrates, and 100 mg/d of spironolactone. His acute symptoms resolved and his BP within 1 month was 130 to 140/70 to 80 mm Hg. His hypertension control has remained adequate for several years on the same regimen.

Case 2

P.R., a 34-year-old white woman, had resistant hypertension since age 26 years (treatment: 50 mg/d of atenolol, 480 mg/d of diltiazem, 10 mg/d of doxazosin, and 20 mg/d of fosinopril). She presented with severe headache, nausea, vomiting, confusion, blurred vision, and a BP of 204/130 mm Hg. Pertinent findings on examination included a 2/6 systolic murmur. After correction of K⁺ (3.8 mEq/L), AC was 32 ng/dL and PRA 0.3 ng/mL/h. Primary hyperaldosteronism was confirmed with urine aldosterone of 23.7 µg/24 h (24-h urinary Na⁺ > 200 mEq/day). A CT scan of the adrenal glands showed a left 2-cm lesion with characteristics typical of an adenoma. A left adrenalectomy was performed and pathologic evaluation confirmed an aldosteronoma. By postoperative year 6, she remained normotensive without medications. Subsequent follow-up has revealed fairly normal office and home BP.

Case 3

J.M., a 37-year-old white man with hypertension since the age of 20 years, had refractory hypertension (150/95 mm Hg) for 5 years despite treatment with 300 mg of labetalol twice daily, 150 mg/d of irbesartan, 20 mg/d of quinapril, 80 mg/d of furosemide, 40 mg/d of minoxidil, potassium supplements, and 0.1 mg of clonidine at night. He presented with BP of >230/120 mm Hg associated with severe headache, confusion, chest pain, and dyspnea. Intravenous nitroprusside was required for initial hypertension treatment. A CT of the head, electrocardiogram with cardiac enzymes, renal scintigraphy, and urinary catecholamines were all without abnormality. Laboratory data included SCr of 0.8 mg/dL, K⁺ of 3.5 mEq/L, AC of 37.3 ng/dL, and PRA of 0.2 ng/mL/h. Aldosterone excess was confirmed with oral sodium loading (urine aldosterone of 36.7 µg/24 h, urinary Na⁺ of 271 mEq/d). A CT of the adrenal glands revealed bilateral adrenal nodules (left nodule measuring 0.8 cm and right nodule measuring 2.0 cm). Adrenal vein sampling under cosyntropin stimulation did not suggest lateralization. He was treated with a multidrug regimen including 100 mg/d of eplerenone, 10 mg/d of amlodipine, 320 mg/d of valsartan, 200 mg/d of metoprolol XL, and 4 mg/d of doxazosin, achieving reasonable BP control at a 6-month follow-up (128/80 mm Hg).

Case 4

G.W., a 49-year-old white man with untreated hypertension diagnosed 18 months before admission, presented with a BP of 250/150 mm Hg associated with headaches and encephalopathy. Physical findings included arteriovenous narrowing and nicking, a small retinal flame hemorrhage, and on cardiac examination a 2/6 apical heart murmur was heard. An electrocardiogram met criteria for left ventricular hypertrophy and CT scan of the head and lumbar puncture were normal. His symptoms improved with BP normalization during the next 48 h. Laboratory data on admission included a K⁺ of 2.8 mEq/L, SCr of 1.2 mg/dL, AC of 15.3 ng/dL, and PRA of 0.8 ng/mL/h. Repeat laboratory data included K⁺ of 3.9 mEq/L, AC of 30.9 ng/dL, and PRA of 0.6 ng/mL/h. An adrenal CT revealed “bilateral hyperplasia.” Adrenal vein sampling did not suggest lateralization based on cortisol-corrected PAC lateralization ratio of <3:1. The patient was subsequently started on 50 mg/d of eplerenone plus 10 mg/d of amlodipine and 200 mg/d of metoprolol XL with significant improvement in BP (144/88 mm Hg) within 2 months.

Case 5

N.F., a 39-year-old obese white man, presented with confusion, expressive aphasia, retinal hemorrhages, right sided hemiparesis, and a BP of 230/130 mm Hg. His hypertension was controlled with intravenous nitroprusside and the neurologic deficits resolved completely. Initial laboratory data included a K⁺ of 3.3 mEq/L, SCr of 1.3 mg/dL, AC of 15.0 mg/dL, with PRA of 0.1 ng/mL/h. Repeat data included K⁺ of 4.3 mEq/L, AC of 25.3 ng/dL, and PRA of 0.1 ng/mL/h and additional secondary causes of hypertension were ruled out. Primary aldosteronism was confirmed with oral sodium loading (urine aldosterone of 35.6 µg/d and urinary Na⁺ 265 mEq/d). A CT of the adrenal glands was normal and adrenal vein sampling showed bilateral aldosterone excess. The patient was discharged on 50 mg/d of spironolactone, 300 mg/d of metoprolol XL, 10 mg/d of amlodipine, and 160 mg/d of valsartan. He developed painful gynecomastia requiring substitution of spironolactone with 50 mg/d of eplerenone. His BP was well controlled at a 12-month follow-up (138/84 mm Hg).
Case 6

S.C., a 73-year-old African-American man with hypertension and type 2 diabetes for 33 years, was admitted with BP of 200/120 mm Hg associated with congestive heart failure and mild renal insufficiency. Before admission, his medications included 25 mg/d of hydrochlorothiazide, 1.2 mg/d of clonidine, 100 mg/d of atenolol, 100 mg/d of losartan, and K+ supplements. Laboratory data included K+ of 3.2 mEq/L and Scr of 1.3 mg/dL, AC of 22.5 ng/dL, and PRA of 0.2 ng/dL. A CT of the adrenal glands revealed bilateral hyperplasia. He refused further evaluation and therapy with 50 mg/d of spironolactone was added to his regimen. There was a significant improvement in BP control (120 to 130/60 to 70 mm Hg) for several years.

Case 7

R.B., a 53-year-old white man with type 2 diabetes for 30 years and hypertension, was treated with 40 mg of lisinopril twice daily, 3.125 mg of carvedilol twice daily, 40 mg/d of furosemide, 10 mg/d of amlodipine, and 80 mEq/d of K+ supplementation. A hospitalization was required for BP of 200/100 mm Hg and congestive heart failure. Laboratory data included Scr of 1.2 mg/dL, K+ of 2.2 mEq/L, AC of 60.7 ng/dL, and PRA of less than 0.1 ng/mL/h, urine aldosterone of 50.2 µg/d, urinary Na+ of 158 mEq/d, and K+ of 302 mEq/d. Additional urinary tests for catecholamines, metanephrines, and cortisol were within reference range. An adrenal CT revealed two left adrenal nodules, 2 cm and 1.4 cm, respectively. He has so far declined adrenal vein sampling. His BP control (110/70 mm Hg) has remained excellent for 8 months on medical therapy including 25 mg/d of spironolactone, 25 mg/d of carvedilol, 10 mg/d of amlodipine, 40 mg/d of lisinopril, and 80 mg/d of furosemide.

Case 8

R.K., a 66-year-old white man with type 2 diabetes mellitus, presented for evaluation of a 20-year history of resistant hypertension. He was hospitalized twice for hypertension emergencies including one for a left parietal cerebrovascular accident associated with BP of 200/100 mm Hg and another admission with encephalopathy, headache, and BP of 250/150 mm Hg. Present medications include 100 mg/d of atenolol and 40 mg/d of lotensin. Physical examination findings include retinal arteriovenous narrowing with copper-wire changes and a fourth heart sound on cardiac examination. Laboratory data includes a K+ of 4.4 mEq/L, Scr of 1.1 mg/dL, AC of 24.2 ng/dL, and PRA less than 0.1 ng/mL/h. Urinary catecholamines and metanephrines were within reference ranges. Hyperaldosteronism was confirmed with urine aldosterone of 23.0 µg/d and urinary Na+ of 175 mEq/24 h. An adrenal CT was normal and the patient declined adrenal vein sampling. He was continued on 50 mg/d of eplerenone, 10 mg/d of

Table 1. Biochemical characteristics of 8 patients with primary hyperaldosteronism associated with hypertensive emergencies

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Diagnosis of Hypertension (y)</th>
<th>Age at Diagnosis of Hyperaldosteronism (y)</th>
<th>Peak Blood Pressure (mm Hg)</th>
<th>Serum Aldosterone (ng/mL)</th>
<th>Plasma Renin Activity (ng/mL/h)</th>
<th>Urinary Sodium (mEq/d)</th>
<th>Urinary Aldosterone (µg/24 h)</th>
<th>K+ (mEq/L)</th>
<th>Scr (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.L.</td>
<td>38</td>
<td>52</td>
<td>200/170</td>
<td>29.0</td>
<td>0.3</td>
<td>4.0</td>
<td>NA*</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>P.R.</td>
<td>26</td>
<td>34</td>
<td>120/140</td>
<td>37.0</td>
<td>0.2</td>
<td>2.9</td>
<td>200</td>
<td>NA*</td>
<td>0.8</td>
</tr>
<tr>
<td>J.M.</td>
<td>20</td>
<td>37</td>
<td>210/130</td>
<td>37.0</td>
<td>0.2</td>
<td>2.9</td>
<td>210</td>
<td>NA*</td>
<td>0.8</td>
</tr>
<tr>
<td>G.W.</td>
<td>47</td>
<td>39</td>
<td>210/130</td>
<td>37.0</td>
<td>0.2</td>
<td>2.9</td>
<td>210</td>
<td>NA*</td>
<td>0.8</td>
</tr>
<tr>
<td>S.C.</td>
<td>40</td>
<td>73</td>
<td>210/130</td>
<td>37.0</td>
<td>0.2</td>
<td>2.9</td>
<td>210</td>
<td>NA*</td>
<td>0.8</td>
</tr>
<tr>
<td>R.B.</td>
<td>46</td>
<td>66</td>
<td>250/150</td>
<td>30.9</td>
<td>0.2</td>
<td>2.9</td>
<td>210</td>
<td>NA*</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* NA - not available
lotensin, 80 mg/d of telmisartan, and 12.5 mg/d of hydrochlorothiazide with marked improvement in BP control (120/70 mm Hg).

Discussion
This case series (Table 1) illustrates that patients with clinical primary aldosteronism can have severe hypertension and develop hypertensive emergencies. It also illustrates some of the difficulties in the confirmatory testing and diagnosis of PA in the setting of acute hypertensive crisis when sodium loading may not be safe. All of our patients had elevated AC and suppressed PRA despite having a hypertensive emergency and antialdosterone treatment was quite effective in lowering BP.

Of our eight hypertensive emergency cases, three had confirmed primary aldosteronism (diagnostic sodium loading tests) and five were deemed probable cases based on their elevated ARR and excellent responses to antialdosterone blockade (sodium loading considered unsafe or indeterminate). Of the five “probable” cases, two had elevated urinary aldosterone levels but urinary sodium was not sufficient (>200 mEq/24 h) to establish the diagnosis. The remaining three cases did not have confirmatory testing performed because of their clinical status. The mean ARR for the confirmed and probable cases were 119 and 117, respectively. Hypertensive encephalopathy was a concomitant diagnosis in five cases and congestive heart failure was present in three cases. The average time between initial diagnosis of hypertension and subsequent diagnosis of primary aldosteronism was 15.6 years.

The diagnosis of PA in our “probable” cases can be debated. A critical observer may label these cases as low renin hypertension because we did not complete definitive sodium loading. We used a random AC of 15 ng/dL as one criterion for a positive screening test but this is more sensitive in a sodium loaded state. However, in the acutely ill patients such as ours, it is impractical to do sodium loading. Our second criterion for a positive screening test was an elevated ARR of more than 40. Although the optimal ratio for a positive test is debated, a AC/PRA ratio ≥20 to 30 and a AC ≥15 after sodium loading provides excellent sensitivity in screening. The PRA has a profound effect on the ARR and small changes may lead to false-positive screening tests. Despite these limitations we believe our probable cases actually have PA.

The BP-lowering effects observed in our patients with aldosterone blockade have also been reported in patients with refractory hypertension with and without PA. Nishizaka et al25 reported that the addition of low doses of spironolactone to a multdrug regimen in patients with resistant hypertension led to a marked decline in BP and allowed reduction of other medications. Furthermore, the benefit was seen in patients with and without a diagnosis of PA. Likewise Ouzan et al26 reported a marked benefit in BP for 25 patients with essential hypertension who had spironolactone added at a dose of 1 mg/kg/d. It should be noted, however, that hypertensive crises are associated at times with secondary hyperaldosteronism and in that setting aldosterone blockade may be less useful.

Primary aldosteronism should obviously be suspected in patients with hypertension and hypokalemia, resistant hypertension, and hypertension associated with adrenal masses. It should also be considered as shown by our cases in the setting of a hypertensive emergency. Traditional diagnostic sodium loading may be difficult in this group of patients.

References