Primary Aldosteronism in a Patient with an Aldosterone-Producing Adenoma

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We describe an unusual patient presenting with a history of refractory hypertension and hypokalemia. Initial screening tests for adrenal hypertension were consistent with primary aldosteronism and an abdominal computed tomography scan showed an 8-mm left adrenal mass. However, adrenal venous sampling revealed markedly suppressed plasma aldosterone in the left adrenal vein but increased plasma aldosterone in the right adrenal vein. Therefore, on the basis of the clinical, radiographic, and laboratory findings, we concluded that the patient had a nonfunctioning adrenocortical adenoma on the left and an aldosterone-producing adrenocortical adenoma on the right, with the aldosteronoma resulting in hypertension and hypokalemia. Right adrenalectomy decreased the hypertension and corrected the hypokalemia. The right adrenal contained a 7-mm nodule microscopically consistent with the diagnosis of a cortical adenoma. The case highlights key steps and potential pitfalls in the evaluation of adrenal hypertension.

Indexing Terms: hypertension • hypokalemia • adrenal vein sampling • idiopathic hyperaldosteronism

The syndrome of “primary” aldosteronism, referring to chronic autonomous aldosterone secretion existing independently or at least semi-independently of the renin-angiotensin system, is characterized by hypertension, hypokalemia, suppressed plasma renin activity (PRA) and increased plasma aldosterone concentration (PAC). This syndrome, sometimes referred to as “low-renin hyperaldosteronism,” is distinguished from hyperaldosteronism secondary to high renin activity in conditions such as cirrhosis, nephrotic syndrome, and congestive heart failure, in which a decreased effective intravascular volume results in prolonged stimulation of renin secretion. Estimates of the incidence of primary aldosteronism vary from 0.05% to 2% of the hypertensive population. The diagnosis is generally made in the third to fifth decades of life.

The most common adrenal lesion responsible for primary aldosteronism, based on findings at operation, is a solitary adrenocortical aldosterone-producing adenoma (APA). Bilateral adrenal hyperplasia, or idiopathic hyperaldosteronism (IHA), constitutes the majority of the remainder of cases. Other subtypes, including glucocorticoid-suppressible hyperaldosteronism and aldosterone-producing adrenocortical carcinoma, make up a very small number of cases of primary aldosteronism. More recently, two additional, less common subtypes have been described. One, primary adrenal hyperplasia, is characterized by hyperplastic adrenal glands that resemble IHA morphologically, but the patients exhibit features of APAs such as responses to physiological maneuvers, 18-hydroxycorticosterone (18-OHB) excess, and response to unilateral or subtotal adrenalectomy. The other subtype, termed aldosterone-producing renin-responsive adenoma, appears as an APA morphologically and in response to unilateral adrenalectomy, but responds to physiological maneuvers in the same manner as the hyperplastic glands.

The signs and symptoms of primary aldosteronism are often subtle; therefore, this diagnosis should be considered when spontaneous hypokalemia or easily provoked hypokalemia (hypokalemia induced by the administration of large amounts of NaCl for 3-5 days, or more severe hypokalemia than that expected during usual treatment with diuretics) is observed in a patient with hypertension. Hypokalemia appears to be the most consistent detectable biochemical manifestation in primary aldosteronism, and is seen in ~80-90% of patients with this disorder. Hypokalemia is a consequence of renal potassium wastage, as a result of the action of aldosterone on the renal distal tubule. A detailed account of the mechanisms of action of aldosterone, at the molecular level, is provided by Horisberger and Rossier. Although low serum potassium may result in weakness, paresthesias, intermittent paralysis, nocturnal polyuria and polydipsia, numerous patients with spontaneous hypokalemia have no symptoms. Metabolic alkalosis, also seen frequently in primary aldosteronism, occurs secondary to persistent hypokalemia.

The clinical syndrome of primary aldosteronism must be considered in a patient with refractory hypertension and persistent hypokalemia. Young et al. outlined a diagnostic approach that can be best viewed as three consecutive studies. These include screening tests, which consist of serum and urine potassium, PRA, and PAC-PRA ratio; positive screening tests strongly support the diagnosis of autonomous aldosterone hyperse-
cretion. Second, the diagnosis of primary aldosteronism needs to be confirmed by a suppression test that demonstrates nonsuppressible aldosterone excretion rates in conjunction with normal cortisol excretion. Finally, once the diagnosis of primary aldosteronism is confirmed, it is important to distinguish between APA and IHA to provide appropriate therapy.

Case Report

A 61-year-old white man with a history of refractory hypertension for at least 7 years, in addition to persistently low potassium concentrations, was admitted to our hospital for further evaluation for endocrine (adrenal) hypertension. At that time, he reported occasional paresthesiae in both lower extremities, but denied muscle weakness, paralysis, or other specific complaints. The patient had taken various antihypertensive medications in the past, and more recently was taking diltiazem, 120 mg (orally, twice a day), and enalapril, 20 mg (orally, four times a day).

Physical examination revealed a well-nourished, non-Cushingoid man with a blood pressure of 178/96 mm Hg and no other remarkable physical findings. Pertinent laboratory findings included a leukocyte count of \( 7.5 \times 10^9/L \) (reference range, 4–11), hemoglobin 137 g/L (140–180), and hematocrit 0.40 (0.40–0.52). Results of the chemistry panel were as follows: Na\(^+\) 141 mmol/L (135–145), K\(^+\) 3.5 mmol/L (3.5–5), Cl\(^-\) 101 mmol/L (95–106), CO\(_2\) 29 mmol/L (24–30), glucose 7.3 mmol/L (4.4–6.0), urea nitrogen 4.3 mmol/L (2.9–9.3), creatinine 106 \( \mu \)mol/L (53–106), total protein 64 g/L (63–86), albumin 36 g/L (35–45), calcium 2.2 mmol/L (2.2–2.6), phosphate 0.84 mmol/L (0.8–1.5), and uric acid 0.33 mmol/L (0.2–0.5). Liver enzymes were within the normal range. An electrocardiogram showed sinus bradycardia at 48 beats/min, with U waves in leads V\(_2\)–V\(_3\).

Upright serum aldosterone and PRA values obtained before admission were 0.74 nmol/L and 0.62 nmol/L per hour, respectively (refer to reference ranges below). A subsequent PRA measurement was 0.3 nmol/L per hour. Results of thyroid-function tests, as well as urine cortisol and metanephrine concentration, were within normal limits. Tests performed upon admission, with the patient on a liberal sodium diet, were as follows: serum aldosterone supine 0.69 nmol/L (0–0.44), upright 0.94 nmol/L (0.1–0.86); and PRA supine <0.15 nmol/L per hour (0.15–1.77), upright <0.15 nmol/L per hour (1–3.1). In addition, the concentration of 18-OHB (supine) was 1.24 nmol/L. Urinary aldosterone excretion was 80 nmol/24 h (6–53), urinary K\(^+\) was 87 mmol/24 h (normal <30 mmol/24 h for serum K\(^+\) <3.6 mmol/L), and urinary Na\(^+\) was 150 mmol/24 h. Enalapril was temporarily discontinued at least 3 weeks before these tests. An abdominal computed tomography (CT) scan showed an 8-mm low-density lesion in the left adrenal gland. Bilateral adrenal venous sampling was subsequently performed to confirm the presence of a functioning (aldosterone-producing) adenoma in the left adrenal gland. The results of the bilateral adrenal vein samples, obtained by catheterization on two separate occasions, are summarized in Table 1. In addition to aldosterone, cortisol was measured (without corticotropin stimulation) simultaneously to confirm the adrenal vein as the site of sampling. As shown in Table 1, aldosterone concentrations in the right adrenal vein were significantly increased, in conjunction with suppressed concentration in the left adrenal vein. However, the findings were felt to be inconclusive because the cortisol measurement from the left adrenal gland suggested that the sample was probably not from the adrenal vein; therefore, bilateral adrenal venous sampling was repeated. Repeat sampling showed similar results, with increased aldosterone on the right, and suppressed aldosterone in the left adrenal vein.

Subsequently, this patient underwent a right adrenalectomy. Examination of the adrenal gland revealed a 7-mm nodule at the periphery of the gland, which microscopically appeared consistent with a cortical adenoma. Postoperatively, the patient did well. His blood pressure remained high at 150/85 during the immediate 24–36 h following surgery; however, it decreased to 115/76 on the third postoperative day. His serum potassium returned to normal (4.4–4.5 mmol/L) immediately after surgery. At subsequent clinic visits, his blood pressure has remained under good control, and the dose of his single antihypertensive medication is continuing to be tapered. In addition, his serum potassium remained within the normal range. PAC—6 weeks after right adrenalectomy was 0.22 mmol/L (0.1–0.86).

Materials and Methods

PRA was measured with the Clinical Assay Gamma Coat \(^{[25]}\) I plasma renin radioimmunoassay kit (Inectar Corp., Stillwater, MN). The determination involves radioimmunoassay of angiotensin I generated at pH 6 (maleate buffer) in the presence of phenylmethylsulfonyl fluoride at 37 ± 2 °C (7). The serum 18-OHB determinations were performed by Endocrine Sciences (Calabasas Hills, CA), using RIA after paper chromatography by the method of Martin et al. (8). The urine free cortisol determinations were performed by Smith-Kline Beecham (Van Nuys, CA), utilizing the liquid chromatographic method of Canalis et al. (9).

Discussion

As outlined in an excellent review article by Young et al. (3), hypokalemia in conjunction with inappropriate kaliuresis, as well as low PRA and a high PAC, are features of the initial screening evaluation that suggest primary aldosteronism. On the basis of their experience with cases of primary aldosteronism at the Mayo Clinic, Young et al. further specify that a PRA <2.3 nmol/L per
hour and a ratio of PAC (in nmol/L) to PRA (in nmol/L per hour) >0.78 are highly suggestive of primary aldosteronism and should, therefore, be considered as positive screening tests requiring further investigation to confirm the diagnosis. When at least two of these findings (spontaneous hypokalemia with inappropriate kaliuresis, PRA <2.3 nmol/L per hour and PAC-PRA ratio >0.78) are detected upon initial screening, further investigation is required to confirm the diagnosis, and involves some form of aldosterone suppression test to identify nonsuppressible aldosterone excretion in conjunction with normal cortisol excretion. Aldosterone suppression testing, which involves evaluating whether or not the zona glomerulosa of the adrenal gland is suppressible in response to physiological regulators (e.g., expansion of the extracellular fluid volume), can be achieved through oral administration of NaCl followed by measurement of urinary aldosterone, or by intravenous NaCl loading and measurement of serum aldosterone. Unlike normal individuals under similar conditions, patients with primary aldosteronism will fail to suppress aldosterone in the face of NaCl loading and secondary volume expansion. Suppression of urinary aldosterone to <0.28–0.42 µmol/24 h or PAC to <0.28 nmol/L, when measured under conditions of high dietary salt intake, is considered a normal response; patients with primary aldosteronism will not demonstrate this response.

Once the diagnosis of primary aldosteronism has been confirmed, it is essential to identify and localize the adrenal lesion because the therapy is distinctly different for APA and IHA, the two lesions that make up the majority of cases of primary aldosteronism. The treatment of choice for patients with APA is unilateral total adrenalectomy. Hypokalemia is often corrected immediately after surgery, whereas hypertension may persist for as long as 4–6 weeks after surgery, requiring at least one antihypertensive medication to adequately control blood pressure. Although the vast majority of patients with an APA will show some improvement in control of blood pressure after the operation, the overall long-term cure rates with unilateral adrenalectomy appear to be ~70% (3). In contrast, the cure rate of hypertension in patients with IHA after unilateral or bilateral adrenalectomy is only ~20% (3). Therefore, the current recommended treatment for IHA, as well as for poor surgical candidates, is pharmacological therapy, with the use of a potassium-sparing agent (e.g., spironolactone) as the first-line drug of choice. Second-step agents, which include calcium channel antagonists, thiazides, and angiotensin-converting enzyme inhibitors, may also be required in some patients to achieve adequate blood pressure control. Interestingly, the response to spironolactone, a specific competitive antagonist of aldosterone, in a patient with hypertension may be an important predictor of the ultimate outcome of therapy (10). Administration of spironolactone in large doses (400 mg) for 3 weeks to patients with hypertension caused by either an APA or a lesion that mimics the APA response to unilateral adrenalectomy reduces the blood pressure significantly. However, it often does not significantly affect blood pressure in patients with IHA or in those in whom hypertension is unresponsive to surgical removal of the adrenal gland. Therefore, patients with APA who do not respond to spironolactone are not likely to be cured of hypertension by surgical intervention (10).

Among the various tests that can be performed to distinguish APA from IHA are adrenal CT scanning, magnetic resonance imaging, adrenal radionuclide scanning (iodectintigraphy), posture studies, measurement of 18-OHB, and adrenal venous aldosterone sampling. Bilateral adrenal venous sampling for measurement of aldosterone concentration remains the most accurate test in differentiating between APA and IHA, although it can be technically difficult to perform. Adrenal CT scanning has become more popular as an initial study, especially with the advent of newer, high-resolution scanners that can detect and localize a microadenoma larger than 7 mm (11). On CT scanning, patients with IHA will have either normal-appearing adrenal glands or changes consistent with bilateral nodular hyperplasia (12). The smallest APAs accurately localized with adrenal CT in a series (143 surgically treated cases) at the Mayo Clinic have been 7-mm microadenomas (3). In the same series, a mean diameter of 1.8 cm was reported, with 19% of the surgically treated cases of APA having an adenoma ≤1 cm in diameter. Young et al. (3) concluded that a unilateral adrenal macroadenoma (>1 cm) seen by CT is highly suggestive of APA, so that further evaluation to distinguish between APA and IHA is probably not necessary. Bilateral APA or unilateral APA with contralateral nonfunctioning adenoma is less common and may confuse the picture. Furthermore, because a small percentage of the normal population has benign nonfunctioning adenomas, and nonfunctioning adenomas are detected in ~1% of patients who undergo a CT scan, the finding of a small adrenal mass by CT in a patient with presumed primary aldosteronism may not be diagnostic of an APA (3). In fact, the accuracy of CT scanning in patients with primary aldosteronism has been estimated to be only 73–90% (3). Therefore, it has been proposed that the finding of a unilateral adrenal microadenoma (<1 cm) by computer-assisted adrenal imaging requires additional evaluation through a postural study, measurement of 18-OHB, or bilateral adrenal venous sampling to confirm the probability of APA (3).

The measurement of plasma 18-OHB with the patient in the supine position is often performed in conjunction with postural studies in a further attempt to distinguish APA from IHA. The steroid 18-OHB is thought to be either the immediate precursor of aldosterone or a byproduct of the aldosterone biosynthetic pathway. In their series, Young et al. (3) found that patients with APA generally had 18-OHB >2.75 nmol/L, whereas those with IHA typically had 18-OHB <2.75 nmol/L. In understanding the postural study, it is important to recall that aldosterone is regulated by the renin-angiotensin-aldosterone axis in normal individuals, and upright posture will increase aldosterone as a result of
increased renin production. In APA, renin is suppressed and, therefore, no increase in PAC with upright posture between 0800 and 1200 is seen. Instead, there may be a paradoxical decrease in PAC as a consequence of the diurnal decrease in corticotropin, a hormone to which adenomas appear to be quite sensitive. In contrast, IHA appears to be much more sensitive to small changes in angiotensin II, which occur when subjects assume upright posture. Therefore, although renin is suppressed, it appears that upright posture increases renin sufficiently to increase PAC. A measurement of blood cortisol must be obtained concurrently to confirm the normal diurnal decrease in corticotropin. Thus, if a decrease in cortisol is seen after a patient is upright and ambulatory for 4 h in the morning, then an increased aldosterone is more meaningful. Although postural studies and measurement of 18-OHB may be helpful in distinguishing APA and IHA, some physicians may be more reluctant to perform these studies when a CT scan reveals an adenoma in a patient with primary aldosteronism, because the patient may have APA even though results from these studies suggest IHA, as can be seen in a renin-responsive APA (13). More recently, the presence of excess 19-nor-deoxycorticosterone, a hypertensinogenic mineralocorticoid that is equipotent with aldosterone and independent of the renin-angiotensin system, has been investigated in patients with APAs and may prove to be a valuable additional probe in attempting to distinguish APA from IHA (14).

Bilateral adrenal venous sampling in this patient was crucial in the evaluation of adrenal hypertension secondary to a functioning (aldosterone-producing) adenoma, especially in view of the suspicious findings revealed through CT. The results of bilateral adrenal venous sampling in conjunction with those found on CT scanning suggested the presence of a nonfunctioning adenoma in the left adrenal gland in addition to a microscopic aldosterone-producing adenoma in the right adrenal gland, with the aldosteronoma resulting in refractory hypertension and persistent hypokalemia. The excellent response of this patient's blood pressure and hypokalemia to unilateral adrenalectomy strongly supports the diagnosis of an aldosterone-producing adenoma.

Axelrod and Vickery (13) presented the case of a 52-year-old man with persistent hypertension and hypokalemia who was found to have a unilateral renin-responsive APA, as an illustration of the difficulty that can arise in distinguishing APA from IHA. The patient was found to have primary aldosteronism from a renin-responsive APA, an uncommon lesion that mimics an APA morphologically and in response to unilateral adrenalectomy but which responds to physiological maneuvers in the way that hyperplastic glands do in IHA. Therefore, although a large adenoma is seen on CT scanning and strongly suggests the presence of an APA, the results of functional studies, including measurement of plasma 18-OHB and postural studies, will be most consistent with IHA.

Our case brings to attention yet another difficulty that may be encountered in distinguishing APA from IHA. As previously discussed, the simultaneous occurrence of a unilateral APA and contralateral nonfunctioning adrenal adenoma may confuse the picture, perhaps more so when the functioning adenoma is microscopic and cannot be detected with a high-resolution CT scanner. The results for 18-OHB (1.25 nmol/L; reference range <2.75 nmol/L) and postural studies (~80% increase in PAC with upright posture) were more consistent with IHA; however, these results should be interpreted with caution, because concurrent results for cortisol at 0800 and 1200 were not obtained. Interestingly, had the results of 18-OHB and postural studies in this case been more consistent with APA, they might have been misleading because the etiology of primary aldosteronism might have been readily attributed to the left adrenal mass seen on CT scanning. The correct diagnosis for the patient we describe would probably not have been made in the absence of adrenal venous sampling. Bilateral adrenal venous sampling for measurement of aldosterone concentration, one of the first tests used to distinguish APA and IHA, is still the most accurate test in differentiating these two lesions. However, it can be technically difficult, is invasive, and depends on the proficiency of the radiologist. Catheterization of the right adrenal vein can be very difficult, given the anatomy of the relatively small right adrenal vein, which drains directly into the inferior vena cava, as opposed to the left adrenal vein, which drains into the larger left renal vein before entering the vena cava. Technical difficulties of the procedure, although uncommon, include bleeding at the groin site of catheter entry as well as an allergic reaction to contrast dye. Additional risks of adrenal venous sampling include adrenal vein thrombosis, ablation of the adrenal gland secondary to overinjection of contrast material, and, in patients with an adrenal pheochromocytoma, the possibility of a hypertensive crisis due to the transient, significant release of catecholamines into the circulation (15). However, the use of nonionic contrast material along with gentle injections of contrast dye has considerably reduced such risks. The normal adrenal venous aldosterone concentration ranges from 2.75 to 11 nmol/L. The adrenal venous aldosterone concentration on the side of the APA may be from 27.8 to 278 nmol/L and, more importantly, the ratio of ipsilateral (site of the lesion) to contralateral aldosterone concentration is usually >10:1 (5). Although corticotropin-stimulated concentrations of adrenal venous cortisol have been obtained at some institutions to further verify the placement of the catheter in the adrenal vein as well as to attempt to establish a diagnosis in an unresolved, nondiagnostic case, corticotropin stimulation is not routinely performed in this institution unless there remains a question of the diagnosis.

In conclusion, the syndrome of primary aldosteronism should be considered in a patient with refractory hypertension and hypokalemia and, accordingly, should be thoroughly investigated through a series of screening
tests, followed by an aldosterone suppression test to confirm the diagnosis. Thereafter, distinguishing unilateral from bilateral adrenal disease is essential to provide appropriate therapy. However, as we have discussed, several difficulties can be encountered in distinguishing APA from IHA; ultimately, the careful consideration of all clinical, radiographic, and laboratory findings is necessary in arriving at the correct diagnosis.

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References