Case Report

ISSN 1738-5997 (Print) • ISSN 2092-9935 (Online)
Electrolyte Blood Press 14:11-15, 2016
http://dx.doi.org/10.5049/EBP.2016.14.1.11

Hypokalemic Hypertension Leading to a Diagnosis of Autosomal Dominant Polycystic Kidney Disease

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Received: January 15, 2016
Accepted: April 8, 2016
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Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disease. Hypertension is common and occurs before decline in renal function. However, the coexistence of hypertension and hypokalemia is rare in ADPKD patients. We report on a 32-year-old woman with secondary aldosteronism. Magnetic resonance imaging of the renal arteries revealed multiple cysts of varying sizes in both the kidneys and the liver, compatible with ADPKD. Increased renin-angiotensin-aldosterone system activity was secondary to cyst expansion. After initiation of angiotensin II receptor blocker, her blood pressure was controlled without additional requirement of potassium.

Key Words: Angiotensin receptor antagonists, Autosomal dominant polycystic kidney disease, Hyperaldosteronism, Hypertension, Hypokalemia

Introduction

Secondary hypertension is defined as hypertension that results from an identifiable etiology. Only 5-10% of hypertension cases are thought to have a secondary cause, whereas the majority of hypertensive patients have essential (idiopathic or primary) hypertension[1]. Because hypertension can be controlled by specific medication or surgery, it is thus important to identify certain clinical suspicions that could suggest the secondary form of hypertension.

One of the clinical features indicative of secondary hypertension is hypokalemia due to mineralocorticoid excess. Hypokalemia may be combined with metabolic alkalosis and excessive urinary sodium excretion. Disorders with mineralocorticoid excess can be divided into three categories. First, in the high aldosterone-low renin category, the diagnosis is primary aldosteronism. High aldosteronehigh renin, known as secondary aldosteronism, includes malignant hypertension, renovascular hypertension, and renin-producing tumor. In the low aldosterone-low renin category, the diagnoses to consider are apparent mineralocorticoid excess, congenital adrenal hyperplasia, Cushing's syndrome, deoxycorticosterone-producing tumor, exogenous mineralocorticoid intake, and Liddle's syndrome.

Autosomal dominant polycystic kidney disease (ADPKD) is a common hereditary renal disease affecting approximately 12.5 million people worldwide. It is characterized by the gradual growth of multiple renal cysts, hypertension and, eventually, end-stage renal disease (ESRD), accounting for 5-10% of ESRD cases[2,3]. Hypertension is the early and frequent manifestation of ADPKD. It appears in 50-70% of cases before a noticeable reduction in glomerular filtration, with the average age of onset of 30 years[4]. ADPKD in patients with hypertension leads to a great and rapid loss of renal function[5]. Up-regulation of the reninangio-

tensin-aldosterone system (RAAS) plays a major role in the pathogenesis of hypertension in ADPKD. However, the coexistence of hypertension and hypokalemia is very rare in ADPKD patients. We illustrate a case with hypertension and hypokalemia who was finally diagnosed with ADPKD and successfully corrected hypokalemia and hypertension with angiotensin II receptor blocker (ARB).

Case Report

A 32-year-old Asian female was referred to an endocrinologist for evaluation of hypertension and hypokalemia. Blood pressure of 170/120 mmHg was found during a routine annual examination. She was asymptomatic and did not take diuretic, liquorice or herbs. She did not have diarrhea, vomiting, history of chronic alcohol intake or toxin exposure. Her parents had hypertension starting in late adulthood. She had no family history of stroke, renal disease, periodic paralysis or hypokalemia. Her electrolytes were notable for serum potassium of 3 mmol/L (mEq/L) with spot urine potassium concentration of 23 mmol/L. Despite taking a combination of antihypertensive drugs of amlodipine 10 mg daily and atenolol 50 mg daily, her blood pressure remained 130/100-150/110 mmHg.

On examination, the patient's blood pressure was 134/96 mmHg and heart rate was 104 beats/min. Clinical examination findings were unremarkable except for being overweight according to Asian criteria (body mass index, 23.4 kg/m^2). No Cushingoid appearance was detected. Auscultation showed no renal bruit. Laboratory evaluation showed hypokalemia and normal renal function [sodium 140 mmol/L (136-145), potassium 3.31 mmol/L (3.5-5.1), chloride 106 mmol/L (98-107), carbon dioxide 26.4 mmol/L (22-29), blood urea nitrogen 19 mg/dL (7-18), creatinine 0.77 mg/dL (0.51-0.95)]. Urinalysis showed 3-5 red blood cells per high-power field, without protein and glucose. She required up to 1.5 g of oral potassium chloride daily to maintain normokalemia. Supine plasma renin activity and aldosterone concentrations were 1.41 ng/mL/h (reference range, supine position 0.23-3.33 and seated position 0.36-3.84 ng/mL/h) and 25.2 ng/dL (reference range, supine position 1-16 and seated position 2.5-31.5 ng/dL), with an aldosterone/renin ratio of 17.87 (primary hyperaldosteronism, ratio >20; secondary hyper- aldosteronism, ratio ~10). Clinical and laboratory data favored a diagnosis of secondary aldosteronism. Magnetic resonance imaging of renal arteries was initially planned to exclude renal artery stenosis, but the examination revealed multiple cysts of varying sizes in both the kidneys and the liver, consistent with ADPKD (Fig. 1). There was no adrenal mass or renal artery stenosis.

After the diagnosis of ADPKD had been established, the patient received valsartan 80 mg daily without further requirement of potassium (Table 1). After a 4-year follow-up, her blood pressure was controlled within the normal range, and she had no further episodes of hypokalemia.

Discussion

We demonstrate a patient with ADPKD discovered by work-up of secondary aldosteronism. In addition, we show the benefit of ARB for treatment of hypertension and hypo-

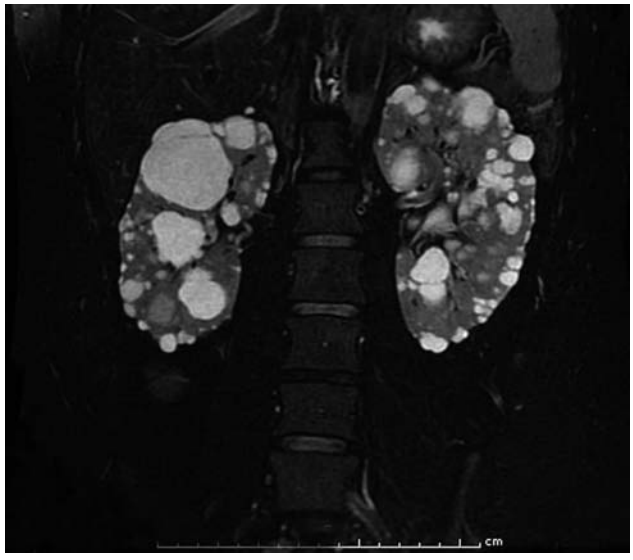

Fig. 1. Magnetic resonance imaging of the renal artery revealed innumerable cysts, causing diffuse enlargement of both kidneys. The cysts ranged from subcentimeter size to the largest diameter of 5.3 cm. The largest cyst is seen at the upper pole of the right kidney, which had thin septation. Also, there were multiple small hepatic cysts ranging from tiny to 1.1 cm in diameter (not shown). Renal arteries and adrenal glands were normal (not shown).

Table 1. Summary of serum electrolyte before and after initiation of angiotensin II receptor blocker (ARB)

	At presentation	After initiation of ARB			Reference range
		1 month	3 months	1 year	
Serum sodium	140	134	136	140	136-145 mmol/L
Serum potassium	3.31	3.96	3.78	3.87	3.5-5.1 mmol/L
Serum chloride	106	103	104	107	98-107 mmol/L
Serum bicarbonate	26.4	25.5	23.8	21.9	22-29 mmol/L
Treatment (daily dose)	Amlodipine (10 mg) Atenolol (50 mg) KCl (1.5 g)	Valsartan (80 mg)	Valsartan (80 mg)	Valsartan (80 mg)	

ARB, angiotensin II receptor blocker; KCl, potassium chloride.

kalemia.

Increased blood pressure in patients with ADPKD have been attributed to several causes, including activation of the RAAS, increase in sympathetic nervous system activity, endothelial dysfunction, increased endothelin-1, and arterial stiffness. The most important factor is the activation of the RAAS, possibly caused by renal vascular compression by cyst expansion, leading to bilateral renal ischemia. Plasma renin activity and plasma aldosterone concentration in hypertensive patients with ADPKD were significantly higher than in matched patients with essential hyperten- sion[6]. In addition, immunohistochemical studies and clinical studies support a major role of the intrarenal RAAS in the pathogenesis of hypertension in patients with ADPKD. Activation of the RAAS may enhance renal cyst formation and enlargement by means of its mitogenic effects[7].

However, hypokalemia is a rare manifestation in ADPKD patients. Renal impairment due to ADPKD could mask hypokalemia. Additionally, activation and dysregulation of the intrarenal RAAS is sufficient to result in increased blood pressure without affecting the circulating RAAS[8]. In our patient, normal plasma renin activity and a low aldosterone/renin ratio favored a diagnosis of secondary aldosteronism. The coexistence of hypertension and hypokalemia in secondary aldosteronism is an uncommon presentation in ADPKD patients; only two cases have been reported[9,10]. There are other case reports of ADPKD complicated by the coincidence of primary aldosteronism[11-15]. The diagnosis included hyperaldosteronemia and hyporeninemia. Even though the identification of adrenal adenoma may be obscured by adjacent renal cysts, adrenal venous sampling can confirm the site of aldosterone-producing adenoma. Excessive aldosterone aggravates cyst formation and/or progression[16,17]. Among patients with primary aldosteronism, either adrenalectomy or spironolactone resulted in the abrogation of newly developed renal cysts on follow-up ultrasonographic imaging[17].

Considering that RAAS plays an important role in the pathophysiology of hypertension in ADPKD, treatment with angiotensin-converting enzyme inhibitor (ACEI) or ARB has been suggested to be the first-line of treatment. Increased renal plasma flow and decreased renal vascular resistance were found in hypertensive patients with ADPKD after administration of enalapril[6]. This rationale was supported by recent data from large, randomized, double-blind, placebo-controlled Halt Progression of Polycystic Kidney Disease (HALT-PKD) trials[18,19]. Theoretically, dual therapy of ACEI and ARB should improve renal outcomes by circumventing the compensatory feedback response that generates more angiotensin II when a single blocker is used. Data from HALT-PKD trials showed that combination therapy was not more effective than monotherapy with an RAAS blocker[18,19]. The role of the direct renin inhibitor, aliskiren, is not yet established in ADPKD patients; however, it could be relevant given that this is the only RAAS inhibitor which also reduces plasma renin[9,10]. To date, there is no head-to-head comparison study between ACEI and ARB for the renal or cardiovascular outcomes in ADPKD patients. There is no available evidence on the potential benefits of adding an aldosterone

antagonist to ACEIs or ARBs.

Previous reports of ADPKD cases with secondary aldosteronism were managed with a direct renin inhibitor (aliskiren)[9,10], while our case was managed with ARB. Hypertension was successfully controlled without a potassium supplement in all cases. ARB blocks the binding of angiotensin II to the angiotensin-1 receptor, which leads to increments in plasma renin activity and levels of angiotensin I and angiotensin II. However, this elevation of precursors does not overcome the receptor blockade, as evidenced by a persistent decrease in both blood pressure and plasma aldosterone concentrations[20]. Either ACEI or ARB, not only direct renin inhibitor, could be the drug of choice for managing ADPKD with secondary aldosteronism. However, further study is required to compare the effectiveness of hypertension treatment among RAAS- blocking agents in ADPKD with secondary aldosteronism.

In summary, hypertension with hypokalemia is an uncommon presentation that clinicians should be aware of in ADPKD. RAAS activation plays an important role in the pathogenesis of hypertension in ADPKD patients. Understanding the exact mechanism of hypertension will contribute to effective blood pressure control, as observed in this case.

Conflict of interest statement: None declared.

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