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jraas

Journal of the Renin-Angiotensin-Aldosterone System
0(0) 1–7

DOI: 10.1177/1470320312452767
jra.sagepub.com
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Delayed diagnosis of primary aldosteronism in patients with autosomal dominant polycystic kidney diseases

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Abstract

Hypertension is a frequent early manifestation of autosomal dominant polycystic kidney disease (ADPKD). Several mechanisms can cause hypertension in ADPKD patients, although, primary aldosteronism (PA) as a possible manifestation of hypertension in ADPKD is extremely rare. We retrospectively reviewed the Taiwan Primary Aldosteronism Investigation (TAIPAI) database, which listed a total of 346 patients diagnosed with PA. Of these 346 patients, only three cases of concurrent PA and ADPKD were identified. These patients presented with hypertensive crisis and hypokalemia, and subsequent testing revealed aldosterone-producing adenomas (APAs) that were removed by laparoscopic adrenalectomy. Postoperatively, aldosterone-renin ratios (ARRs) and potassium levels normalized, and blood pressure improved. The diagnosis of PA in ADPKD is extremely challenging because multiple renal cysts can obscure the identification of adrenal adenomas, and ADPKD is associated with hypertension in almost all cases.[1] Because of frequent delays in the diagnosis of PA in ADPKD patients, future prospective studies to screen PA in hypertensive ADPKD patients may be necessary to evaluate the exact prevalence of coexistence of PA and ADPKD.

Keywords

Primary aldosteronism, autosomal dominant polycystic kidney disease, hypokalemia, hypertensive crisis

Introduction

Hypertension presents as a common early clinical symptom in 50–75% of autosomal dominant polycystic kidney disease (ADPKD) patients.[2] The pathogenesis of hypertension in ADPKD includes intrarenal activation of the renin-angiotensin system, primary disruption of polycystin function in the vasculature, impaired nitric oxide-related vasorelaxation, increased sympathetic nerve activity, increased plasma endothelin-1 concentrations and insulin resistance.[3] Primary aldosteronism (PA), caused by nonsuppressible hypersecretion of aldosterone and accompanied by low renin levels, occurs in approximately 10% of patients with mild to moderate hypertension and 20% of patients with resistant hypertension.[4] The excessive production of aldosterone in PA is associated with a higher incidence of cardiovascular events than essential hypertension (EH).[5] Hypokalemia, a major characteristic of PA, can result in target organ damage[6] and aggravated hypertension. Although these two etiologies are secondary to hypertension in the middle-aged population, the occurrence of PA in ADPKD patients has not been frequently reported in the published literature.

Here, we describe three ADPKD patients who experienced hypertensive crises and hypokalemia associated with PA.

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Materials and methods

We performed a retrospective study at National Taiwan University Hospital and its affiliated hospitals, and we reviewed the Taiwan Primary Aldosteronism Investigation (TAIPAI) database. Over the 13-year period (January 1995 to December 2007), 346 patients were diagnosed with PA. Of these 346 patients, only three had concurrent PA and ADPKD. All medical records of these three patients were assessed. Demographic, clinical, laboratory and pathological information were collected. Clinical information included family history, comorbidities, therapeutic management and outcomes. Additionally, we search the PubMed database to identify studies reporting the coexistence of PA and ADPKD using "Hyperaldosteronism" and "Polycystic Kidney, Autosomal Dominant" as the medical subject heading (MeSH) terms.

Case reports

Patient 1: A 26-year-old woman was referred from a local medical department (LMD) because of hypertensive crisis (blood pressure (BP) of 210/120 mmHg) after suffering from untreated hypertension for three years. Computed tomography (CT) images obtained at the LMD revealed a 0.5 × 0.5 cm mass on the left adrenal gland and multiple homogenous cysts on both kidneys. After considering her family history of ADPKD, simple cystic kidney disease was excluded. Initially, hypokalemia (K = 2.8 mEq/L) was noted, and a series of tests showed a high plasma aldosterone-renin ratio (ARR); plasma ARR, defined as the ratio of plasma aldosterone concentration (PAC)* to plasma renin activity (PRA)*, was 103 (PAC = 31 ng/dL, PRA = 0.3 $ng \cdot mL^{-1} \cdot h^{-1}$). A post-captopril test revealed a high ARR of 310 (PAC = 31 ng/dL, PRA = 0.1 $ng \cdot mL^{-1} \cdot h^{-1}$), confirming the diagnosis of PA. However, further image analysis did not reveal the presence of any adrenal masses, and the patient was lost to follow-up after her BP became relatively stable at 130/90 mmHg. Two years later, she returned to our hospital with persistent hypertension (BP = 200/120 mmHg) and a headache. Testing demonstrated a high ARR of 1120 (PAC = 112 ng/dL, PRA = 0.1 $ng \cdot mL^{-1} \cdot h^{-1}$) and the presence of hypokalemia (K = 3.1 mEq/L), while CT revealed the presence of a hypodense mass on the left adrenal gland. Refractory hypertension (BP = 224/140 mmHg) was noted despite the patient's use of four antihypertensive drugs. The adrenal tumor then was removed via left laparoscopic adrenalectomy, and aldosterone-producing adenoma (APA) was confirmed at tumor pathology. Two weeks after surgery, the patient's BP normalized (100/80 mmHg) without medications, and her serum potassium, PAC and PRA were normal (Table 1).

Patient 2: The second patient was a 36-year-old woman with a history of ADPKD and a 12-year history of hypertension, including an episode of pre-eclampsia due to chronic hypertension during her first pregnancy at age 31. Two years later, hypertensive crisis (BP = 240/130 mmHg) and hypokalemia (K = 1.7 mEq/L) developed during her second pregnancy. To control her hypertension, the following medications were prescribed: spironolactone (one pill, twice a day) and amlodipine (one pill, once a day). Three years after her second pregnancy, resistant hypertension (BP = 214/140 mmHg) with blurred vision developed, with an ARR of 51.9 (PAC = 40 ng/dL, PRA = 0.77 $ng \cdot mL^{-1} \cdot h^{-1}$); a post-captopril test confirmed an elevated ARR of 410 (PAC = 41 ng/dL, PRA = 0.1 $ng \cdot mL^{-1} \cdot h^{-1}$). CT imaging revealed a 1.5-cm hypodense tumor on the left adrenal gland, and PA (APA type) was histopathologically confirmed by laparoscopic adrenalectomy. One month after the operation, mild hypertension (BP = 141/107 mmHg) persisted and 4 mg doxazosin was prescribed to be taken once daily for control of the patient's elevated BP. PRA, PAC and serum potassium levels normalized (Table 1).

Patient 3: A 54-year-old woman with a 10-year history of ADPKD and resistant hypertension had suffered a left putamen hemorrhage seven months before the referral. She developed extreme hypertension (BP = 205/105 mmHg, hypertensive retinopathy) and hypokalemia (K = 2.0 mEq/L) three months before the referral. Screening tests for PA showed an ARR of 560 with a PAC of 56 ng/dL and a PRA of 0.1 $ng \cdot mL^{-1} \cdot h^{-1}$. An abdominal magnetic resonance imaging (MRI) revealed a 2-cm nodule on the right adrenal gland, and the patient was referred to our hospital for a right laparoscopic adrenalectomy; histopathology showed a cortical adenoma. One month after the operation, BP, serum potassium and ARR returned to normal.

PRA was measured by the generation of angiotensin I in vitro using a commercially available radioimmunoassay (RIA) kit (Stillwater, MN, USA) according to the manufacturer's instructions. The mean (SD) intra-assay and interassay coefficients of variation for the PRA assay were 1.9% (5.0%) and 4.5% (5.2%), respectively. The concentration of PAC was measured by RIA using commercial kits (Aldosterone Maia Kit, Adaltis Italia S.p.A., Bologna, Italy), as previously described.[7,8] Normal PRA levels were between 1–5 $ng \cdot mL^{-1} \cdot h^{-1}$. The minimal detectable concentration (sensitivity) was 0.018 ng/tube.[9]

Discussion

We have reported three cases of ADPKD involving APAs. In the TAIPAI study cohort, the coexistence of ADPKD and PA is rare.[10–12] Approximately 60% of ADPKD patients present hypertension before renal function becomes impaired.[1] Although most clinicians consider the intrarenal activation of the renin-angiotensin-aldosterone system (RAAS) to be the main pathogenesis of hypertension in ADPKD patients, there may be additional causes of hypertension. Identifying ADPKD-affected individuals with modifiable secondary hypertension, such as aldosteronism,

Table 1. Summary of the 11 patients with concurrent PA and ADPKD.

	P't 1	P't 2	P't 3	4 Bobrie G et al.[13]	5 Bobrie G et al.[13]	6 Bobrie G et al.[13]	7 Saeki, S et al.[14]	8 Gejyo F et al.[15]	9 Rajasoorya et al.[16]	10 Liou HH et al.[17]	11 Hoorn EJ et al.[18]
Age	23/28	24/36	44/54	26/29	40/44	47/49	36/39	30/42	30/36	19/23	37/57
Delayed diagnosis	5 years	12 years	10 years	3 years	4 years	2 years	3 years	12 years	6 years	4 years	20 years
Sex	F	F	F	M	F	F	F	F	M	F	F
BP (mmHg)	210/100	240/130	205/105	224/128	220/130	172/116	166/100	180/100	110/90	180/120	150/90
Serum potassium (mEq/L)	2.8	1.7	2.0	2.1	3.3	> 4	3.3	2.7	1.9	1.9	3.3
Urinary potassium (mEq/day)	33	47	54	100	33	57	NA	NA	NA	42	NA
TTKG *	6.74	7.43	12.76	NA	NA	NA	NA	NA	NA	NA	8.28
Serum creatinine (mg/dL)	0.8	0.9	0.59	1.13	1.06	1.40	0.81	normal	1.27	0.8	
Serum sodium (mEq/L)	144	137	145	NA	NA	NA	NA	NA	NA	NA	146
PH/HCO3	7.41/23.7	7.46/27.9	7.42/29.6	NA	NA	NA	NA	7.45/31.4	7.46/28.4	NA	NA/32.8
PRA * (supine) ($ng{\cdot}mL^{-1}{\cdot}h^{-1}$)	0.3	0.77	0.1	< 0.1	< 0.1	0.51	0.6	0.2	0.3	< 0.3	0.15
PRA (upright) (ng/mL/h)	NA	NA	NA	< 0.1	< 0.1	0.72	NA	NA	NA	NA	NA
Plasma aldosterone (ng/dL)	31	40	56	26.4	15.4	31.5	21.5–37.3	70	66.6	57	53
ARR *	103	51.9	560	>264	>154	61.8	NA	350	222	> 190	353

(Continued)

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Adrenal pathology	cortical adenoma	cortical adenoma	cortical adenoma	adrenal adenoma	bilateral hyperplasia	bilateral hyperplasia	adrenal adenoma	adrenal adenoma	cortical hyperplastic nodules	adrenal cortical adenoma	NA
Treatment	laparoscopic adrenalectomy	laparoscopic adrenalectomy	laparoscopic adrenalectomy	right adrenalectomy	aldactone 2 $mg \cdot kg^{-1} \cdot day^{-1}$ + verapamil 120 mg/day	aldactone 1.2 $mg \cdot kg^{-1} \cdot day^{-1}$	right adrenalectomy	left adrenalectomy	left adrenalectomy	right adrenalectomy	spironolactone 50 mg qd
After treatment											
BP (mmHg)	100/80	141/107	133/88	150/102	144/90	142/98	140/95	NA	120/90	120/80	NA
Serum potassium (mEq/L)	4.3	4.5	4.0	4.4	4.5	4.4	NA	4.0	3.8	4.7	NA
Serum creatinine (umol/L)	NA	NA	NA	1.39	1.09	1.65	NA	NA	1.22	0.7	NA
PRA ($ng \cdot mL^{-1} \cdot h^{-1}$)	1.97	0.8	1.09	1.6	NA	NA	5.2	0.8	NA	1.5	NA
Plasma aldosterone (ng/dL)	29	18	21	2.2	NA	NA	12.2	14.3	NA	7.3	NA
ARR	14.7	22.5	19.3	1.4	NA	NA	2.4	17.9	NA	4.9	NA

PA: primary aldosteronism; ADPKD: autosomal dominant polycystic kidney disease; TTKG: transtubular potassium gradient; PRA: plasma renin activity; ARR: aldosterone renin ratio; NA: not available.

is challenging since multiple renal cysts may obscure the identification of adrenal adenomas. Avoiding delays in diagnosis will permit aggressive BP treatment, early inhibition of the RAAS and decreased cardiovascular risks.[5,6]

Including our three patients, a total of 11 patients with PA and ADPKD have been reported in the literature (Table 1);[13–18] these consisted of two men and nine women. The mean age at diagnosis of PA was 40 years old (range, 23 to 57 years). A characteristic feature in all of these patients was a delay in the diagnosis of PA, on an average seven years after the diagnosis of hypertension. It may not be very different as compared to underdiagnosed PA in the general population because of the variable presentation of PA. Due to the delayed diagnosis, hypertensive crisis or resistant hypertension invariably developed in these patients (the initial mean BP: 187/110 ± 38/15 mmHg).

Retrospectively, several important features provided information to suggest an earlier diagnosis of PA may have been possible in ADPKD patients. Including our three patients, the 11 reported patients with PA and ADPKD presented initially with hypokalemia (mean K = 2.6 ± 0.8 mEq/L), considered to be a "classical" sign of PA arising from persistent aldosterone-mediated potassium secretion in the cortical collecting tubule. In all cases, hypokalemia was identified during the investigation of possible hyperaldosteronism; however, hypokalemia also occurs in ADPKD,[19] resulting in a diagnostic dilemma. Once the coexistence of hypokalemia and resistant hypertension is identified in ADPKD patients, a secondary cause of hypertension should be suspected. Although the exact mechanism of hypertension in ADPKD is controversial, activation of the RAAS is thought to play a major role in the development of hypertension in ADPKD.[20] Chapman et al.[2] reported PRA was significantly higher in hypertensive patients with ADPKD compared to patients with EH.

To the best of our knowledge, all of the reported ADPKD patients with PA had PRAs of less than 0.77 $ng \cdot mL^{-1} \cdot h^{-1}$, with an average of 0.31 ± 0.22 $ng \cdot mL^{-1} \cdot h^{-1}$, and their ARRs were greater than 50, with an average of 216 ± 158 (Table 1).[13–18] Considering the rare coexistence of ADPKD and PA in our TAIPAI study cohort, a more liberal criterion of initial PRA and ARR levels for further confirmation of PA may be appropriate (Figure 1) .

Screening for PA can benefit both the patient and clinician, particularly in cases where hypertension is severe and/or resistant to treatment; in this situation, the removal of APAs can allow effective controlling of BP. Eight of 11 patients underwent adrenalectomy with cortical adenoma pathology (Table 1). Three patients received drug treatment. Postoperatively, most of the patients had improved BP (132/92 ± 16/9) and laboratory parameters (PRA, 1.85 ± 1.54 $ng \cdot mL^{-1} \cdot h^{-1}$; PAC, 15 ± 9 ng/dL; ARR, 12 ± 9). Furthermore, several clinical studies have demonstrated that excess aldosterone contributes to the development and progression of cardiovascular diseases.[4] In addition to aldosterone-induced target organ inflammation and fibrosis, aldosterone has been linked to components of metabolic syndrome, including hypertension, insulin resistance and dyslipidemia.[21–24] The detrimental effects of aldosterone may expose patients to a greater risk of cardiovascular diseases, but the long-term effects of aldosterone on ADPKD patients are currently unknown.

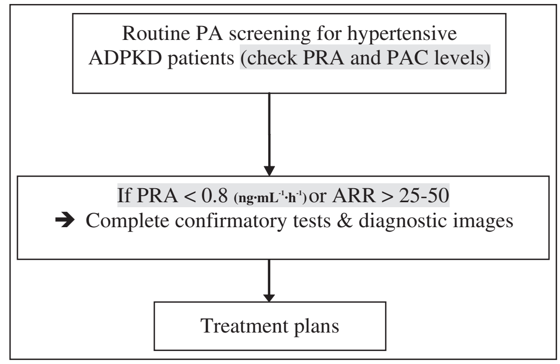

Figure 1. Management of hypertension in ADPKD patients. PA: primary aldosteronism; PRA: plasma renin activity; PAC: plasma aldosterone concentration; ADPKD: autosomal dominant polycystic kidney disease.

Until now, the mechanisms of aldosterone-induced renal cyst formation have not been elucidated. Hypokalemia has been shown to increase cyst formation in rat models;[25] furthermore, as Torres et al.[26] described, chronic hypokalemia in humans is accompanied by enhanced renal cytogenesis and may lead to interstitial scarring and renal insufficiency. Renal cysts also have been reported to develop in potassium-depleted human subjects in which primary or secondary hyperaldosteronism was present. Though these studies do not prove causality, these interactions of PA and ADPKD warrant further investigation. After treatment of PA, monitoring the change in cyst size/number may help explain the interaction between PA and ADPKD; in addition, further studies are necessary to determine if the progression of ADPKD is modified or reversed by treatment of PA.

The low occurrence of PA with ADPKD in our cohort may have resulted from our strict selection of ADPKD patients with hypokalemia and hypertensive crisis for screening. In the general population, Rossi et al.[27] reported that hypokalemia was found in 50% of patients with APA, and APA constituted only about one third of all PA, with idiopathic hyperaldosteronism (IHA) accounting for the remaining two thirds, of whom about 15% were hypokalemic. The finding of three cases of APA among 346 subjects may be the tip of the iceberg of PA as a whole. The real prevalence of PA in ADPKD may approach 5–10% with more relaxed diagnostic criteria. If hypokalemia were to be used as a strict criterion for screening PA, the majority of the PA patients would have been missed. Routine screening of ARR in hypertensive ADPKD patients may be a solution. However, the cost implication should be considered before we have more supporting evidence. Delayed diagnosis of PA in patients with ADPKD puts patients at a greater risk of cardiovascular morbidity/mortality, which can be avoided if PA is detected early. Future studies of screening PA in hypertensive ADPKD patients may be necessary to evaluate the exact prevalence of coexistence of PA and ADPKD.

Conclusions

Here, we reported the cases of three ADPKD patients with PA who presented with hypokalemia and hypertensive crisis. Because of the frequent delays in the diagnosis of PA in ADPKD patients, future studies of screening PA in hypertensive ADPKD patients may be necessary to evaluate the exact prevalence of coexistence of PA and ADPKD.

Funding

This study was supported by The Ta-Tung Kidney Foundation and Taiwan National Science Council (grant NSC 100-2314-B-002-147-MY3, NSC 100-2314-B-002-119-) and 98-N1177, 99-N1408, 100-N1776 from NTUH, and NTUH-TVGH Joint Research Program (VN9803, VN9906 and VN10009).

Conflict of interest

None declared.

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