

Normotensive presentation in primary aldosteronism: A report of two cases

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Abstract

Normotensive patients with primary aldosteronism (PA) are relatively rare. Herein, we report two patients with normotensive PA and present a literature review to improve an understanding of the disease. Patient 1, a 56-year-old man, presented with recurrent hypokalemia that lasted for more than 2 years. Patient 2 was a 33-year-old man who presented with sexual dysfunction and was diagnosed with a prolactinoma combined with adrenal insufficiency and hypogonadism. Neither of these patients had hypertension that was detectable on repeated manual measurements. In both patients, a typical biological profile of PA was demonstrated that included hypokalemia with kaliuresis, elevated plasma aldosterone concentration (PAC), suppressed plasma renin concentration, and a high aldosterone-to-renin ratio. Both patients did not have sufficiently suppressed PAC on the saline infusion test, confirming the diagnosis of PA. Computed tomography of the adrenal gland and adrenal venous sampling suggested an aldosteronoma, which was confirmed by lateralized hypersecretion of aldosterone. After removal of the benign adenoma, the biochemical abnormalities were corrected. As hypertension is not necessarily a sign of PA, we propose that all patients with hypokalemia should be screened for PA in order to prevent cardiovascular complications while balancing economics and effectiveness.

Keywords

Hyperaldosteronism, prehypertension, hypokalemia, hyperprolactinemia, case report

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Introduction

Primary aldosteronism (PA) is the commonest and most modifiable form of secondary hypertension and occurs due to abnormal excessive aldosterone production from the adrenal glands. The clinical spectrum of PA currently includes not only normokalemic hypertension, which occurs in 60%–90% of PA patients, but also unusual cases of normotensive PA revealed by hypokalemia or by an incidentally discovered adrenal mass.¹ We aim to enhance clinician awareness of this clinical presentation by reporting our clinical experience with two cases of hypokalemia-associated normotensive hyperaldosteronism in male patients.

Case presentation

Patient 1

A 56-year-old married man was hospitalized due to recurrent hypokalemia since more than 2 years following incidental detection on preoperative blood tests prior to a left

popliteal cyst surgical excision. The patient achieved eukalemia following potassium supplementation. After being discharged, the patient repeatedly experienced fatigue and noticed palpebral swelling, which was occasionally accompanied by limb numbness, and without

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Table 1. Biochemical summary of the two patients.

Biochemical data	Patient 1	Patient 2	Normal range
Serum levels of electrolytes			
Na (mmol/L)	145.0	142.6	135.0–145.0
K (mmol/L)	2.91	2.96	3.50–5.50
Cl (mmol/L)	103.8	104.7	96.0–106.0
Ca (mmol/L)	2.16	2.24	2.08–2.60
Blood gas analysis			
pH	7.457	7.393	7.350–7.450
Actual bicarbonate concentration (mmol/L)	28.9	28.5	22.0–26.0
Urinary electrolytes analysis			
24 h Urinary K (mmol/24h)	61.46	61.3	25.0–100.0
24 h Urinary Na (mmol/24h)	245.8	232	150–250
PAC (pg/mL)			
Supine PAC	369.0	345.0	30.0–236.0
Standing PAC	421.0	146.0	30.0–353.0
PRC (uIU/mL)			
Supine PRC	1.5	<0.5	2.8–39.9
Standing PRC	1.4	<0.5	4.4–46.1
ARR			
Supine	246	>690	
Standing	300.71	>292	
Saline infusion test			
PAC before test (pg/mL)	388.0	257.0	
PAC after test (pg/mL)	216.0	144.0	
BP before test (mmHg)	139/88	138/89	
BP after test (mmHg)	139/89	131/89	

PAC: plasma aldosterone concentration; PRC: plasma renin concentration; ARR: aldosterone renin ratio; BP: blood pressure.

associated symptoms of fever, night sweats, diarrhea, vomiting, or dizziness, and no record of hypertension during this period; the lowest recorded serum potassium level was 2.44 mmol/L. The patient had no history of hypertension nor a family history of hypokalemia and hypertension.

On physical examination, clinical and vital parameters (height 180 cm; weight 73 kg; pulse 80 beats/min; and blood pressure 134/89 mmHg) were normal. Repeated blood pressure measurements determined by sphygmomanometry were consistently less than 140/90 mmHg. The 24-h ambulatory blood pressure showed an average value of 126/79 mmHg (daytime 127/80 mmHg; nighttime 124/78 mmHg), but the circadian rhythm disappeared. No other abnormal signs were detected.

Blood biochemistry showed that the patient had persistent hypokalemia (range 2.65–3.41 mmol/L; the latter value was recorded after potassium supplementation), associated with alkalosis (pH 7.457, plasma bicarbonate 28.9 mmol/L) and kaliuresis (24-h urinary potassium 61.46 mmol/24 h). Laboratory findings of suppressed plasma renin concentration and elevated plasma aldosterone concentration (PAC), both in the supine and standing positions, and revealed an extremely high aldosterone–renin ratio (ARR) that indicated a diagnosis

of PA (Table 1). Moreover, during the intravenous administration of 2 L isotonic saline over 4 h in a saline infusion test, there was no detectable suppression of PAC on volume expansion. The above-mentioned results confirmed a diagnosis of PA. The patient underwent further investigations, including computed tomography (CT) scanning of the adrenal gland and adrenal venous sampling (AVS), to differentiate the PA subtype. The adrenal CT contrast-enhanced scan showed a nodular low-density shadow, measuring approximately 12.2 mm × 9.8 mm, in the right adrenal gland and had mild enhancement on contrast injection (Figure 1). AVS was carried out to identify the lateralization of aldosterone secretion. The ratio of higher to lower levels of aldosterone/cortisol ratio in the right and left adrenals was 40.88.

The patient underwent laparoscopic right adrenalectomy, and a gross examination of the specimen showed an approximately 15-mm yellowish mass on cross-section. Postoperative histopathology confirmed the mass as an adrenal adenoma. Postoperatively, the orthostatic ARR (4.47) reverted to normal, as did the electrolyte level (potassium 5.45 mmol/L). Blood pressure values on repeated measurements were persistently less than 140/90 mmHg.

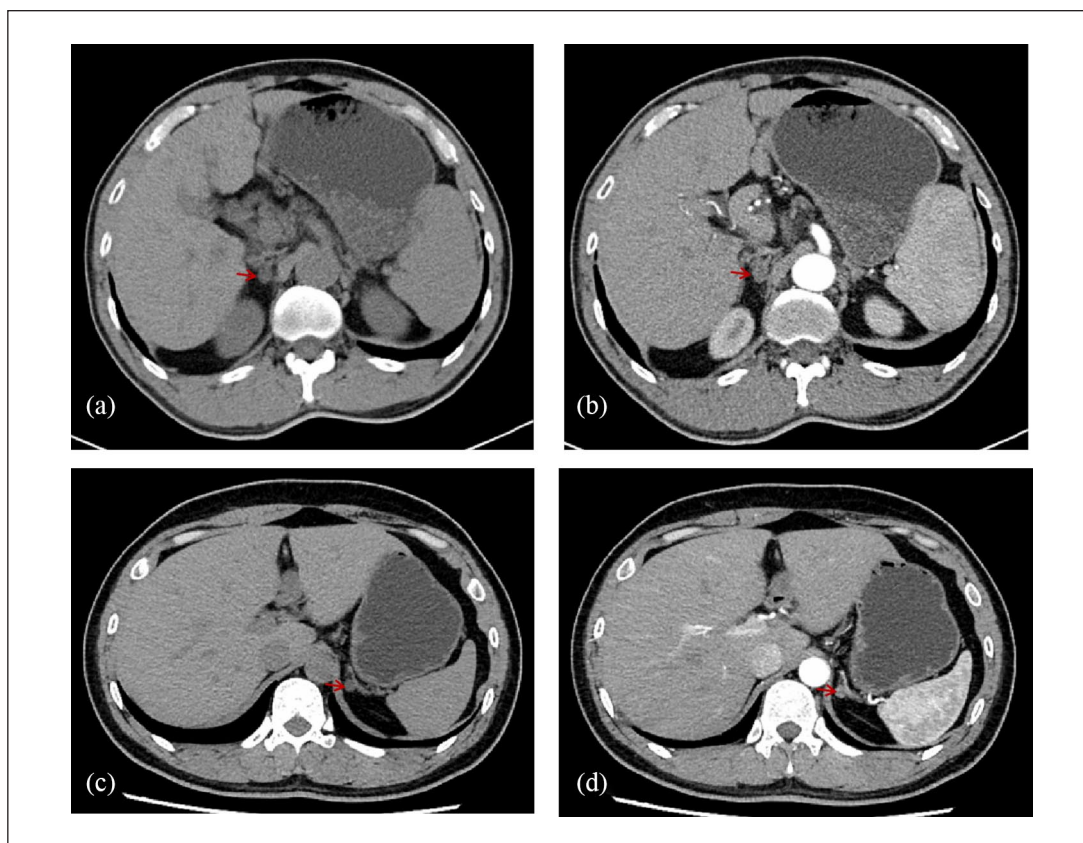


Figure 1. Results of adrenal contrast-enhanced CT of the two patients: (a) adrenal computed tomography scanning of patient 1 showing right adrenal adenoma (pointed by the red arrow), (b) adrenal computed tomography of patient 1 enhancement indicating a mildly intensified right adrenal adenoma (pointed by the red arrow), (c) adrenal computed tomography scanning of patient 2 showing left adrenal adenoma (pointed by the red arrow), and (d) adrenal computed tomography of patient 2 enhancement indicating a mildly intensified left adrenal adenoma (pointed by the red arrow).

Patient 2

A 33-year-old married man presented with a 4-month history of sexual dysfunction associated with fatigue, dizziness, and headache. The patient had no nausea, vomiting, diarrhea, galactorrhea, fever, muscle cramping or weakness, or transient paralysis. The patient reported no previous use of drugs, including diuretics, licorice, herbal supplements, and steroids, and had no history of hypertension. Furthermore, appetite and sleeping pattern were normal. Additionally, the patient was an only child, and there was no relevant family history.

A physical examination revealed an apparently healthy man (height 174 cm; weight 76 kg), with a normal male pattern of facial, body, axillary, and pubic hair distribution and no gynecomastia. The patient was afebrile and had a blood pressure of 131/78 mmHg and a regular pulse of 80 beats/minute. Repeated blood pressure measurements during this hospitalization and from previous annual medical examinations were all within the normal range. Furthermore, there was no evidence of diabetes, reduced muscle strength, malformation, neurological symptoms, or visual disturbance. The results of initial investigations,

including a complete blood count, liver function tests, electrocardiogram, and chest radiograph, were all within the reference range. However, it was interesting that, despite hypokalemia (blood potassium 2.96 mmol/L), the levels of other electrolytes were normal (Table 1).

The patient was diagnosed with and treated for hypogonadism. Sex hormone tests revealed a reduced level of testosterone (5.33 nmol/L, reference range: 5.55–25.17 nmol/L), whereas the prolactin level was considerably elevated (2014.5 mIU/L, reference range: 53.0–360.4 mIU/L). Serum follicle-stimulating hormone (2.4 IU/L; reference range: 0.7–11.1 IU/L) and luteinizing hormone (2 IU/L; reference range: 0.8–7.6 IU/L) were in the normal range. Plasma and urinary osmotic pressures were normal. Routine inspection of growth hormone level showed a normal value, but revealed a decreased level of insulin-like growth factor 1 (67.2 ng/mL, reference range: 115–307 ng/mL). The thyroid function was normal. At 8:00, 16:00, and 00:00 timepoints, values of adrenocorticotropic hormone (ACTH) and plasma cortisol were 14.2, 17.7, and 15.2 pg/mL and 135.51, 116.52, and 41.19 nmol/L, respectively (reference range of ACTH at 8:00: 7.2–63.3 pg/mL, reference range of cortisol at 8:00:

185–624 nmol/L). The gonadotropin-releasing hormone stimulation and insulin-tolerance tests were recommended, but the patient refused to undergo these tests. With a differential diagnosis of hyperprolactinemia, we conducted a magnetic resonance imaging (MRI) of the brain, which showed a 5.5-mm oval, slightly enhancing mass in the left pituitary, without the involvement of the optic chiasma. The combined findings from clinical examination and investigations confirmed a diagnosis of pituitary prolactinoma.

At that time, the symptoms and the test results of the patient did not indicate a direct association with his hypokalemia. Moreover, we had repeatedly confirmed that the patient had significant hypokalemia. With the patient's consent, we conducted further screenings for the cause of hypokalemia while treating sexual dysfunction. The levels of 24-h urine vanilla mandelic acid and glycosylated hemoglobin were normal. Furthermore, as the patient had hypokalemia and kaliuresis (24-h urinary potassium 61.3 mmol/24 h) despite normal levels of other electrolytes, PA was strongly suspected (ARR >292, in the standing position). The PAC was not sufficiently suppressed on the saline infusion test, which confirmed a diagnosis of PA (Table 1). Adrenal contrast-enhanced CT identified an 8-mm left adrenal solid mass with typical features of an adenoma (Figure 1). AVS revealed an aldosterone/cortisol ratio of the left adrenal vein that was approximately 65 times greater than on the right/unaffected side, which definitively confirmed unilateral left-adrenal gland disease. Thus, we diagnosed the patient with PA due to a left-sided aldosterone-producing adenoma (APA).

Surgical treatment was indicated in this patient, and he was transferred to the department of urology for complete tumor resection by laparoscopic left adrenalectomy, and histopathology confirmed a benign adrenal cortical adenoma (10 mm). To prevent an adrenal crisis, the patient preoperatively received intravenous hydrocortisone (50 mg). The steroid replacement dose was tapered as planned (50 mg bid intravenously to oral 10 mg qd7 + 5 mg qd15). Postoperatively, the orthostatic ARR (0.58) normalized with the restoration of normal electrolyte levels (potassium 4.34 mmol/L). Simultaneously, the patient was orally administered bromocriptine 1.25 mg before bedtime for a pituitary prolactinoma and an intramuscular injection of 250 mg testosterone undecanoate for his hypogonadism.

At the 1-month postoperative follow-up, the morning and afternoon levels of cortisol and ACTH were normal, and steroid replacement was discontinued. At the 12-month follow-up, the patient's serum prolactin, testosterone, and ARR in the standing position had returned to normal levels (prolactin 245.9 mIU/L, testosterone 10.52 nmol/L, ARR 0.5). Adrenal CT showed postoperative changes, and pituitary MRI revealed a slightly smaller pituitary

microadenoma (4.6 mm). Postoperatively, the blood pressure remained between 112/66 and 120/79 mmHg.

Discussion

In 1954, Jerome W. Conn first reported PA, which was considered a rare disorder that was only suspected in cases with hypertension and spontaneous hypokalemia. In recent years, with the widespread use of ARR as a screening test, the prevalence of PA has increased from 0.7% to 29.8%, depending on the population that is selected and the diagnostic values that are used.² Currently, some scholars believe that occult hyperaldosteronism constitutes 45%–50% of essential hypertension, of which ≥90% will be attributable to idiopathic hyperaldosteronism (IHA)³; however, APA has a more evident presentation characterized by marked hypertension, spontaneous hypokalemia, and higher levels of plasma aldosterone.⁴ Therefore, it can be speculated that normotensive and normokalemic IHA patients are not rare, although normotensive and hypokalemic patients with APA are even rarer.

Normotensive PA was first reported by Brooks et al.⁵ in 1972, and more than 90 cases have since been reported worldwide (Supplemental File 1). Previously, clinical practice guidelines for PA assumed that hypertension was a hallmark for the diagnosis of PA, although recent evidence has challenged this assumption. Normotensive PA has not been recognized because it is not considered during screening; however, the condition clearly exists, and its prevalence is merely underestimated.⁶ Ito et al.⁷ found that the prevalence of PA was at least 6.8%, 3.3%, and 3.1% in patients with prehypertension, Stage 1 hypertension, and Stage 2 hypertension, respectively.⁸ Therefore, it would appear that PA is not confined to hypertensive patients, but can be a common diagnosis among patients without hypertension.⁹ More than half of the patients with normotensive PA are female, in the age group of 23–84 years. Women who are older than 50 years have a significantly higher ARR than women younger than 50 years; however, the ARR did not significantly differ by age groups in men, which implies a higher incidence of PA in elderly women.¹⁰ Compared to hypertensive PA patients, these patients had significantly lower blood potassium and body mass index, larger tumor diameter, and serum potassium levels that were inversely related to diastolic blood pressure and orthostatic aldosterone levels.¹¹ Most often, the first manifestations are symptoms of hypokalemia (e.g. fatigue, paresthesia, tetany of the hands and feet, and limb paralysis). The imaging investigations mainly reveal adrenal adenoma. Both the patients described in this report were male. The description of the clinical characteristics of these normotensive PA cases was based on a summary of clinical experience, and the specific incidence and molecular mechanism need to be further studied.

The specific mechanism of normal blood pressure in PA patients is unclear. There may be several reasons: (1) Early in the diagnosis of the disease, only hypokalemia is present, and hypertension is not manifested. A Greek case-control study¹² found that PA patients with normal blood pressure were more likely to develop hypertension after 5 years of follow-up than non-PA patients, suggesting that normotensive PA may be an early form of classic PA. Blood pressure of normotensive PA may gradually increase over time. (2) The basal blood pressure of patient is lower before the onset of the disease; therefore, even if the blood pressure is increased, it remains within the diagnostic normal range. (3) The patient's body is less sensitive to the pressor substance, and there may be anterior pituitary hypofunction. (4) The activity of vasodilators (e.g. bradykinin and prostacyclin) in the patient is enhanced, which can prevent hypertension. (5) Genetic and environmental factors contributed to the disease development.

Notably, excessive sodium and insufficient potassium intake are important characteristics of the Chinese dietary structure, and the 24-h urinary sodium values of these two patients confirmed this characteristic. Thus, a normotensive state caused by a related sodium depletion can be ruled out in these two patients. Furthermore, this may also be an important reason why hypokalemia is common among Chinese patients, including those with aldosteronism and essential hypertension.

Patient 1 presented with recurrent hypokalemia of more than a 2-year duration; therefore, the possibility of early disease is unlikely. Clinical examination showed that the thyroid, adrenal, and gonadal functions were normal; therefore, the anterior pituitary hypofunction was ruled out. The patient's basal blood pressure before symptom onset could not be traced, and the postoperative blood pressure was not significantly lower than the preoperative value. Moreover, the patient was an Asian male aged 56 years. Therefore, the normal blood pressure of this patient may be due to the patient's slow response to the pressor substance or due to enhanced vasodilatory activity in the body.

Patient 2 was hospitalized because of sexual dysfunction for more than 4 months. Clinical examination revealed adrenal insufficiency, hypogonadism, and a significant increase in prolactin. In this patient, the coexistence of hypopituitarism seemed to play an important role in preventing the induction of hypertension.¹³ Reduced myocardial effectiveness and excessive prostacyclin secretion have been reported to cause vasodilation and hypotension in glucocorticoid deficiency.¹⁴ Therefore, cortisol hormones may have a permissive effect in mediating mineralocorticoid-induced hypertension through volume expansion, which is due to the putative direct vascular effect or the central nervous system action of aldosterone.¹⁵ Therefore, for hypokalemic patients with complex clinical conditions, we must consider the impact of

underlying diseases on blood pressure, and remember to screen for PA. Besides, reports of APAs coexisting with prolactinoma as part of the multiple endocrine neoplasia type 1 (MEN1) have been infrequently reported in the literature.^{16–22} Williams et al. found that the PRL receptor gene was comparatively highly expressed in APA and that elevated PRL caused by hyperprolactinemia may contribute to the development of PA in cases where APA and prolactinoma coexist.²² DNA analysis of the excised adrenal tumor suggested that adrenal adenoma can be associated with mutations in the *MEN1* gene, and it is possible that the loss of the *MEN1* gene or other chromosome 11 genes can actually cause adrenal adenoma.¹⁶ Considering a variety of phenotypic expression of MEN1 and a limitation of current molecular analysis, periodic follow-up will be needed in this patient with a MEN1-like phenotype.

Nonetheless, PA is a much more heterogeneous disease than indicated by its original classification as a hypertensive disease of endocrine origin. There is a prevalent continuum of renin-independent aldosteronism and mineralocorticoid receptor activity in normotension that ranges from subtle to overtly dysregulated and autonomous. Therefore, hypertension should no longer be considered an essential sign for a diagnosis of PA. From an economic perspective, the determination of the aldosterone level is economical and convenient, and its accuracy has been unanimously recognized. Therefore, we propose that all patients with hypokalemia should be screened for PA to prevent cardiovascular complications.

Author contributions

MJ conceptualized the study, analyzed and interpreted all data, and wrote the manuscript. HY organized clinical data and interpreted the results. ZL, MH, SZ, XX identified, diagnosed, and follow-up the cases. XS conceptualized the study, interpreted study data, and revised the manuscript. All authors read and approved the final manuscript.

Ethical approval and consent to participate

The study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine and was performed in accordance with the Declaration of Helsinki of 2013 for Human Research.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Data accessibility statement

All data generated or analyzed during this study are included in this article.

Supplemental material

Supplemental material for this article is available online.

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