Bojan Marković[1], Mirjana Stojković[1,2], Tamara Janić[1], Jovana Babić[1], Ivana Đurković[1], Nata Joksimović[1], Biljana Nedeljković Beleslin[1,2], Jasmina Ćirić[1,2], Miloš Žarković[1,2]

DIAGNOSTIC UNCERTAINTY IN PRIMARY ALDOSTERONISM

Abstract: Aldosterone is a mineralocorticoid hormone originating from the glomerulosa zone of the adrenal cortex. Its main mechanism of action involves the reabsorption of sodium along with the secretion of potassium and hydrogen ions. It is the final hormonal signal in the renin-angiotensin-aldosterone system, which participates in the regulation of circulating volume and systemic vascular resistance. Hypokalemia and hypertension are key indicators for diagnosing hyperaldosteronism. We present the case of a patient who was diagnosed with hypertension at the age of 30. Hypokalemia was first recorded in his 59th year (2023) with a level of 3.1 mmol/L. The analyzed RAAS markers showed an elevated ALDO/PRA ratio. Computed tomography revealed a change in the right adrenal gland, measuring 9 mm. Given that the baseline aldosterone values were within the normal range for the healthy population, with a suppressed renin activity peak in one sample, primary aldosteronism was suspected. Consequently, confirmatory suppression tests were required to establish the diagnosis.

Keywords: secondary hypertension, aldosteronism, hypokalemia

Introduction:

Aldosterone is a hormone produced by the adrenal cortex and is a key component of the complex renin-angiotensin-aldosterone system (RAAS) (1). Under physiological conditions, it regulates electrolyte balance by increasing sodium reabsorption, which also draws water along with it, and by secreting potassium ions (2). One potential cause of increased aldosterone production is adrenal gland pathology. In

[1] Bojan Marković, Clinic of Endocrinology, Diabetes, and Metabolic Diseases, University Clinical Center of Serbia, Faculty of Medicine, University of Belgrade.

[2] Faculty of Medicine, University of Belgrade, Belgrade.

addition to the RAAS, other regulatory mechanisms, though less influential, include adrenocorticotropic hormone (ACTH), atrial natriuretic peptide (ANP), and dopamine. The majority of patients suffer from primary essential hypertension, with 5 to 10% having secondary endocrine hypertension, including aldosteronism, Cushing's syndrome, or thyroid disease (3). The most common causes of primary aldosteronism are aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (IHA), while familial forms of the disease are less common (4).

A case report:

A 60-year-old male patient was diagnosed with high blood pressure in his 30s. Hypokalemia (K: 3.1 mmol/L) was first detected at the age of 59 and persists even after discontinuation of diuretic therapy. Nephrological evaluation ruled out renal artery stenosis. In an outpatient setting, the RAAS axis was analyzed, which revealed suppressed plasma renin activity (0.7 μIU/mL; reference values: 2.8–39.9). The aldosterone value was within the normal range for healthy individuals (19.3 ng/dL), and the ALDO/PRA ratio was borderline elevated (ARR = 27).

During hospitalization at the Clinic for Endocrinology, Diabetes, and Metabolic Diseases of the UKCS, tests were performed to investigate primary aldosteronism. Computed tomography revealed a small lesion in the right adrenal gland measuring 9 mm, and endocrinological functional tests ruled out autonomous cortisol secretion and catecholamine excess. On aldosterone-neutral therapy, aldosterone values were within the reference range for a healthy population, with suppressed PRA in one sample (ALDO 345.5–254.4, PRA <0.3–5). As a result, the diagnosis of primary aldosteronism could not be excluded. Consequently, confirmatory suppression tests were performed to establish the diagnosis (Tables 1 and 2).

Table 1. Captopril test

Captopril test		
	ALDO ng/dL	PRA ng/mL/h
0 min	30	<0,3
120 min	15,44	0,48

Table 2. Infusion test

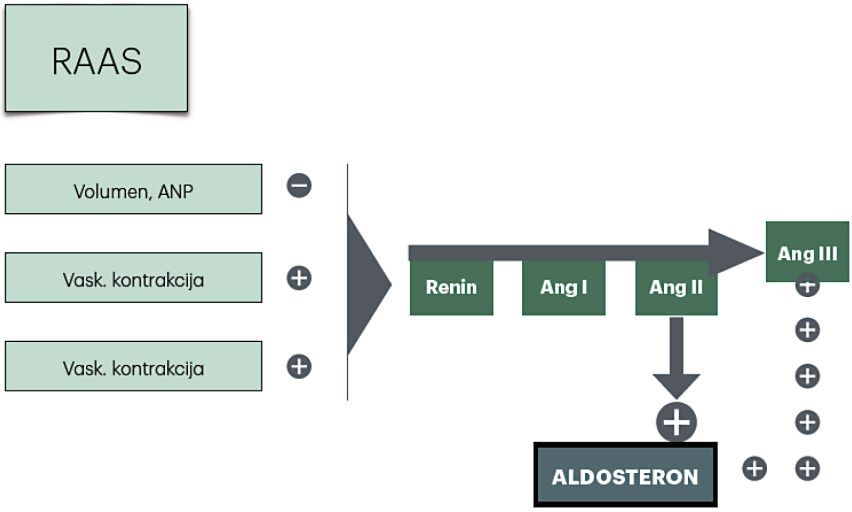
Infusion test		
	ALDO ng/dL	PRA ng/mL/h
0 min	21,83	0,35
30 min	13,59	1,70
60 min	18,46	<0,3
120 min	11,66	<0,3
240 min	10,39	1,1

Atrial fibrillation had previously been diagnosed and was treated with radio-frequency ablation. In 2023, the patient experienced a myocardial infarction, during which two stents were implanted. A heart ultrasound revealed hypokinesia to akinesia of the basal segment of the septum and the basal segment of the inferoposterior wall (EF 60%). The family history was not significant for early hypertension or cardio cerebrovascular events. The patient is a former smoker.

Discussion:

The mineralocorticoid hormone aldosterone plays a key role in maintaining circulating blood volume and serum potassium concentrations. These processes, through a feedback loop, regulate aldosterone secretion from the glomerulosa of the adrenal cortex (Scheme 1). Aldosterone inhibitors include atrial natriuretic peptide (ANP) and local dopamine, while renin synthesis is activated by reduced circulating volume and beta-adrenergic stimulation of sympathetic nerves (5). Elevated potassium levels inhibit renin synthesis, while directly stimulating aldosterone secretion, which highlights the role of the renin-angiotensin-aldosterone system (RAAS) as a protective compensatory mechanism against hyperkalemia. In contrast, hypokalemia reduces aldosterone synthesis, and diuretics that promote potassium loss influence both plasma renin and aldosterone concentrations. Renin is converted to angiotensinogen, which is then converted to angiotensin I; under the influence of angiotensin-converting enzyme (ACE), angiotensin I is further converted to angiotensin II, which in turn stimulates aldosterone release.

Scheme 1. *RAAS*



The final product of angiotensin II is metabolized in the liver to form angiotensin III, a heptapeptide that also stimulates aldosterone secretion (6). Prostaglandins I2 and E2 play a significant role, and it has been shown that metoclopramide increases aldosterone secretion. Two key factors that lead doctors to suspect aldosteronism are: 1. hypertension, particularly when it occurs at a younger age, and 2. hypokalemia. The predictive value of the presence of both components is 50% (7). In younger patients, primary aldosteronism may be asymptomatic. When symptoms do occur, patients commonly complain of headache, facial flushing, and tinnitus. However, long-term uncontrolled hypertension can lead to vision impairment, altered consciousness, and hypertensive encephalopathy. Hypokalemia can cause fatigue, weakness, constipation, and heart rhythm disturbances, but approximately 60% of people with primary aldosteronism are normokalemic (8). Consequently, it is crucial to recognize this clinical condition due to the many complications that can arise over time.

According to the "Joint National Committee" guidelines, screening for primary aldosteronism (PA) is recommended for all patients with: 1. stage 2 hypertension (>160/100–109 mmHg), stage 3 hypertension (>180/110 mmHg), or resistant hypertension despite multi-drug therapy (>140/90 mmHg); 2. spontaneous hypokalemia or hyperkalemia induced by diuretics; 3. hypertension and adrenal incidentaloma; 4. a positive family history of early hypertension or cerebrovascular events (9). In cases of a family history of stroke before 40 years of age, glucocorticoid-mediated aldosteronism (GPA) should be considered, although this was not the case for our patient.

The most common causes of primary aldosteronism are idiopathic bilateral adrenal hyperplasia (IHA) and adrenal adenomas (APA), with the latter typically being small, aldosterone-producing adenomas (less than 2 cm). There are several key differences between these two clinical entities: 1. APA is surgically curable, while IHA is not; 2. APAs produce higher levels of aldosterone compared to IHA; 3. The consequences and complications are more severe with APA (10, 11). Since our patient had a morphological substrate–specifically, a 9 mm adenoma in the right adrenal gland–along with a history of early-onset hypertension and spontaneous hypokalemia, testing for primary aldosteronism was initiated. Visualization of the adrenal glands is recommended in all patients with confirmed aldosteronism, and magnetic resonance imaging (MRI) is no more informative than computed tomography (CT) in this context (12).

If hypokalemia is present, potassium should be replenished before initiating testing. Afterward, blood samples for aldosterone and plasma renin activity (PRA) or renin should be taken while the patient is on aldosterone-neutral therapy (washout). The ALDO/PRA ratio (ARR) should then be analyzed, as some patients with primary aldosteronism (PA) may have normal values of these hormones (36–48%). The literature suggests a more significant ARR of 20–40 as indicative of possible aldosteronism, while most authors agree that an ARR over 35 has 100% sensitivity and approximately 92% specificity. However, some clinicians also include elevated aldosterone levels, in addition to a positive ARR, as a criterion for diagnosing PA. If the results are inconclusive, as in the case of our patient, additional diagnostic or functional tests–known as confirmatory tests–should be performed. These include oral sodium load, the captopril test, acute intravascular volume expansion (infusion test), and the fludrocortisone test.

In the case of our patient, two suppression tests were performed: first the captopril test, followed by the infusion test. In the captopril test, the patient was given 50 mg of captopril. The test is interpreted based on the fact that, in individuals without primary aldosteronism (PA), aldosterone levels should decrease by more than 20% from the baseline. Specifically, aldosterone values should fall below 15 ng/dL. The guideline “Diagnosis and Management of Primary Hyperaldosteronism in Patients with Hypertension: A Practical Approach Endorsed by the British and Irish Hypertension Society” outlines a stricter criterion, stating that in healthy individuals, aldosterone levels should drop by at least 30% from baseline (i.e., to below 8 ng/dL). Additionally, the ALDO/PRA ratio after 2 hours should be below 30 (13). The sensitivity of the captopril test is reported to be 90–100%, with specificity ranging from 50–80%. In our patient, the baseline aldosterone value was 30.87 ng/dL, and after the captopril test, aldosterone secretion was suppressed to 15.44 ng/dL. Some authors interpret this suppression as excluding the diagnosis of PA, while others do not. Simultaneously, there was an increase in PRA, which would typically argue

against PA. However, caution is needed when interpreting these results, given the still low PRA value.

In the infusion test, the patient is infused with an isotonic saline solution intravenously at 500 mL/h for 4–6 hours. This typically suppresses serum aldosterone to levels <10 ng/dL in healthy individuals, but not in those with primary aldosteronism (PA). However, some authors consider aldosterone suppression in the range of 5–10 ng/dL to be a gray area, while others set the cut-off at 6.8 ng/dL (14, 15, 16, 17). In our patient, aldosterone was suppressed to 10.39 ng/dL, which is considered borderline suppression. A key test in the diagnostic process is the overnight suppression test with 1 mg of dexamethasone, which could suggest glucocorticoid-mediated aldosteronism (GPA). GPA is an autosomal dominant, hereditary form of aldosteronism characterized by "ectopic" aldosterone secretion from the zona reticularis. In this condition, excess mineralocorticoids are regulated by ACTH. Diagnosis of this rare form of the disease leads to treatment with long-term, low-dose corticosteroids.

Treatment of primary aldosteronism (PA) involves either pharmacological therapy or surgical intervention. The first-line pharmacological treatment includes mineralocorticoid antagonists (spironolactone, eplerenone), glucocorticoids, and other potassium-sparing diuretics (such as triamterene and amiloride). Typical doses of spironolactone range from 50–200 mg daily, with blood pressure normalization expected within 4 to 8 weeks. Side effects of spironolactone include gynecomastia, decreased libido, and impotence in men, while women may experience irregular menstrual cycles. Eplerenone (50 mg twice daily) can be used as a substitute for spironolactone; however, it is more expensive and less potent as a mineralocorticoid antagonist. In patients with idiopathic bilateral adrenal hyperplasia (IHA), treatment is typically based on calcium channel blockers and, particularly, angiotensin-converting enzyme (ACE) inhibitors, which reduce the production of angiotensin II. For adrenal adenomas (APA), adrenalectomy is the preferred treatment. However, alternative surgical options being explored include partial adrenalectomy (wedge resection) and adrenalectomy with preservation of the adrenal medulla. In cases where adrenalectomy is contraindicated, several case reports have described the use of percutaneous ethanol injection for APA (18, 19).

Conclusion:

We presented a patient with a diagnosis of hypertension at a younger age and spontaneous hypokalemia. Given the presence of a small 9 mm adenoma on CT, primary aldosteronism, specifically aldosterone-producing adenoma (APA), was initially suspected. After a comprehensive work-up, the following conclusions were made: 1. The patient exhibited occasional suppression of plasma renin activity, with aldosterone levels within the reference range for healthy individuals. 2. The aldoste-

rone/renin ratio (ARR) was elevated. 3. Both the captopril and infusion tests showed aldosterone suppression to the threshold values for these tests. 4. Family history was not significant for hypertension or vascular events, and the overnight dexamethasone test was negative for glucocorticoid-mediated aldosteronism (GPA). Based on the criteria supported by one group of authors, we could exclude primary aldosteronism. However, according to stricter criteria advocated by other authors, these results might still suggest the possibility of autonomous aldosterone production. Despite varying recommendations, adrenal venous sampling would provide the most definitive diagnostic information in cases with ***gray zone*** results.

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