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EVALUATION OF RENIN-DEPENDENT ALDOSTERONISM

Abstract: A 47-year-old female patient with long-standing arterial hypertension and a history of hypertension during pregnancies was referred for evaluation of possible secondary aldosteronism. Initial tests conducted while the patient was on diuretic therapy showed elevated aldosterone and renin levels, suggestive of renin-dependent aldosteronism. Given the potential influence of therapy, a medication washout was performed, and hormonal testing was repeated. The new results showed normal aldosterone and renin levels without hypokalemia, while blood pressure remained stable. The absence of other pathological findings and stable biochemical parameters indicated that the previous hormonal imbalance was most likely due to relative hypovolemia induced by diuretics. Other causes of secondary aldosteronism were ruled out. This case highlights the importance of proper patient preparation for endocrine testing and the need to exclude medications that may affect the interpretation of the RAAS axis. In cases requiring aldosterone-neutral therapy, non-dihydropyridine calcium channel blockers and alpha-adrenergic blockers are preferred. If heart rate is elevated, verapamil can be used.

Keywords: aldosteronism, hypertension

Case Report

A 47-year-old female patient was hospitalized for evaluation of renin-dependent aldosteronism. She had hypertension during both pregnancies – the first at age 25 and the second at age 35, with the second complicated by preeclampsia. During both pregnancies, she was treated with Methyldopa. Afterward, she was placed on continuous antihypertensive therapy (Nebilet Plus). Between 2023 and 2024, she

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experienced blood pressure spikes (160/100 mmHg) accompanied by headaches and chest tightness. She was followed by a cardiologist who added a beta-blocker, a diuretic (indapamide), and a calcium channel blocker (amlodipine). On this therapy, her blood pressure dropped to 80/65 mmHg. Early this year, a CT scan of the abdomen revealed normal adrenal glands.

Hormonal evaluation in outpatient settings (without prior medication washout) showed elevated noradrenaline (87; reference value <79), while other hormone levels were normal. RAAS axis testing showed a resting renin of 44 and stimulated renin of 68 ng/ml (reference <24), aldosterone in rest 610 ng/ml, stimulated 236, with an ALDO/renin ratio of 14 and 11 respectively (reference value <20). Hypokalemia was not observed. A single TSH result was elevated (8.54; reference <4.85), but no L-T4 therapy was initiated. Glycoregulation was normal (HbA1c 5.7%). Echocardiography from November 2023 showed preserved ejection fraction (EF 66%) without significant findings. 24-hour ambulatory blood pressure monitoring showed a non-dipping pattern of systolic BP. Color Doppler of neck vessels revealed initial atherosclerotic changes in the right internal carotid artery and both subclavian arteries.

No other significant personal medical history. The patient wears corrective glasses since childhood. Mother has had hypertension since her 40s; father had a cardiac stent. Former smoker.

Discussion

The renin–angiotensin–aldosterone system (RAAS) plays a central role in blood pressure regulation. It acts through angiotensin and aldosterone to stimulate thirst, sympathetic activity, peripheral resistance, glomerular arteriole constriction, and sodium and water reabsorption. Activation of RAAS leads to potassium and hydrogen ion loss, which, in pathological states, may cause metabolic alkalosis, hypokalemia, and hypertension.

Various endogenous and exogenous substances influence aldosterone secretion: angiotensin II, ACTH, hypokalemia, ANP, beta-blockers, diuretics, and alpha-adrenergic agonists. Therefore, interpretation of the RAAS axis must be done under aldosterone-neutral therapy. Medications must be discontinued before hormonal testing—4 to 6 weeks for mineralocorticoid receptor antagonists and potassium-sparing diuretics, and at least 2 weeks for other drugs. Guidelines recommend using non-dihydropyridine calcium channel blockers and alpha-adrenergic blockers as alternatives. Before sampling renin and aldosterone, hypokalemia should be corrected to prevent suppression of aldosterone secretion.

Primary or essential hypertension occurs in the majority of patients, while 5–10% have secondary hypertension. Key clinical indications for evaluating secondary causes include:

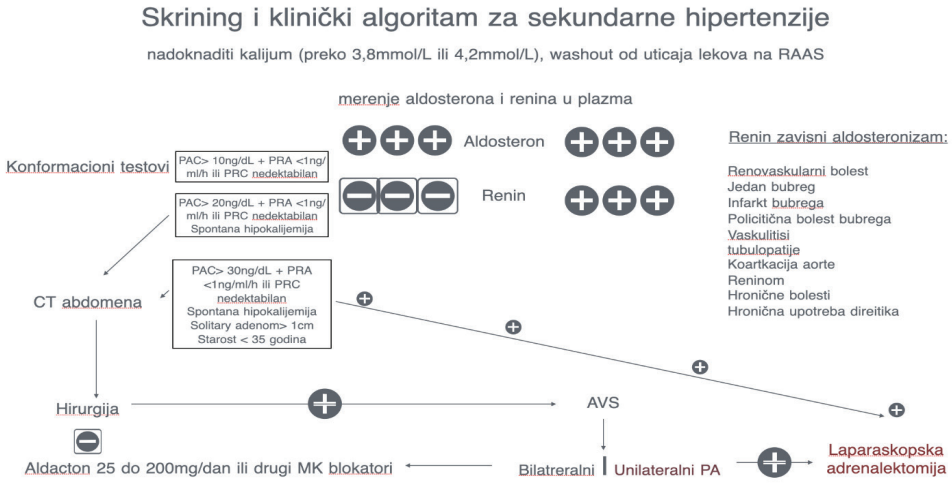
1. Early-onset hypertension (age 30–40)
2. Family history of early-onset hypertension or cardiovascular events
3. Severe hypertension with organ damage
4. Resistant hypertension to 3+ drugs
5. Sudden worsening of previously well-controlled hypertension
6. Hypertension associated with obstructive sleep apnea

From an endocrine perspective, **primary aldosteronism** is the most common cause of secondary hypertension. Other causes include pheochromocytoma, congenital adrenal hyperplasia, Cushing's syndrome, thyroid disorders (hyperthyroidism), and acromegaly. Physical examination should include bilateral BP measurements, lower extremity BP measurement, pulse assessment, and auscultation for murmurs to rule out coarctation of the aorta or mild aortic syndromes. RAAS axis may also be disrupted by **renovascular disease** (atherosclerosis, fibromuscular dysplasia, aneurysms, retroperitoneal fibrosis, tumors), especially in patients with a single kidney. Treatment includes: A) ACE inhibitors or ARBs (note: contraindicated in bilateral stenosis due to risk of acute kidney injury), B) Revascularization procedures. Gold standard for diagnosis is **renal arteriography**, supported by Doppler ultrasound, CT/MR angiography, or renal scintigraphy. Other renal pathologies such as infarctions, vasculitis (especially polyarteritis nodosa), and polycystic kidney disease may also activate baroreceptor mechanisms and lead to secondary aldosteronism.

In rare cases, tumors of juxtaglomerular cells (reninomas), usually benign, cause severe hypertension with high renin and aldosterone. Diagnosis is made via renal vein sampling and treatment is surgical. Other renin-producing tumors include adrenal cortical carcinoma, hepatoblastoma, Wilms tumor, and uterine leiomyomas. **Normotensive secondary aldosteronism** occurs in syndromes like: **Bartter syndrome** (mutated Na-K-2Cl cotransporter): symptoms include polyuria, hypovolemia, osteopenia, nephrocalcinosis, alkalosis, hypokalemia; **Gitelman syndrome** (mutated Na-Cl transporter): hypokalemia, hypomagnesemia, low urinary calcium. Chronic diseases (e.g., heart failure, liver cirrhosis, nephrotic syndrome, chronic diuretic use) cause morphological kidney changes with fewer functioning nephrons and compensatory hyperfunction of remaining nephrons, leading to hypoperfusion and increased aldosterone secretion. Ultimately, **secondary aldosteronism** is a physiological aldosterone increase in response to hypovolemia, while **primary aldosteronism (Conn's syndrome)** is aldosterone production independent of renin. Differentiating the two is essential due to differing treatment approaches (see **Figure 1**).

Key Points

1. **Secondary aldosteronism** is characterized by high aldosterone levels and elevated or unsuppressed renin.
2. Medications affecting the RAAS system must be stopped for **2–6 weeks**, depending on the drug.
3. Allow **liberal salt intake** and correct hypokalemia during testing.
4. Normal aldosterone and renin do not exclude secondary aldosteronism—volume status may mask findings.
5. **Renovascular stenosis** is a primary cause, though some tubulopathies or chronic illnesses may present without hypertension.
6. Measuring **blood pressure in the lower extremities** is advised when suspecting secondary hypertension.



Legenda skraćenica*: PAC – konc. aldosterona u plazmi; PRA – plazma reninska aktivnost; PRC – konc. renina u plazmi; MK – mineralokortikoidni; AVS – adrenalno vensko uzorkovanje; PA – primarni aldosteronizam*

Conclusion

In a patient with early-onset hypertension, suspicion for secondary causes was raised. Initial renin and aldosterone levels suggested secondary aldosteronism. However, since the tests were done while on diuretics and with hypotensive readings, testing was repeated after therapy washout. Follow-up results showed normal aldosterone and

renin levels, indicating the previous RAAS axis imbalance was likely due to relative hypovolemia caused by diuretic use. In this context, renovascular disease remains the only plausible consideration given prior atherosclerotic changes, but throughout the washout period, blood pressure remained stable and other parameters were normal, which supports this interpretation and effectively rules out other causes of renin-dependent aldosteronism.

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