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EVALUACIJA RENIN ZAVISNOG ALDOSTERONIZMA

Sažetak: Pacijentkinja, stara 47 godina, sa dugogodišnjom arterijskom hipertenzijom i anamnezom hipertenzije u trudnoćama, upućena je na ispitivanje mogućeg sekundarnog aldosteronizma. Inicijalne analize, sprovedene pod terapijom diureticima, pokazale su povišene vrednosti aldosterona i renina, što je ukazivalo na renin-zavisni aldosteronizam. S obzirom na potencijalni uticaj terapije, sproveden je terapijski washout i ponovljeno hormonsko testiranje. Novi nalazi pokazali su normalne vrednosti aldosterona i renina, bez prisutne hipokalijemije, dok je krvni pritisak ostao stabilan. Odsustvo drugih patoloških nalaza, uz stabilne biohemijske parametre, ukazuje da je prethodno hormonalno odstupanje najverovatnije posledica relativne hipovolemije izazvane diureticima. S obzirom na to, drugi uzroci sekundarnog aldosteronizma su isključeni. Ovakav slučaj naglašava važnost adekvatne pripreme pacijenta za endokrinološko testiranje i značaj isključenja lekova koji mogu uticati na interpretaciju RAAS osovine. U slučaju potrebe za aldosteron-neutralnom terapijom koriste se nedihidropiridinski blokatori kalcijumskih kanala i alfa-adrenergični blokatori, u slučaju povećanih otkucaja srca može da se koristi verapamil.

Ključne reči: aldosteronizam, hipertenzija.

Prikaz slučaja

Pacijentkinja, 47 godina. Hospitalizovana u cilju ispitivanja renin-zavisnog aldosteronizma. Imala je hipertenziju u obe trudnoće – prva u 25. godini i druga u 35. godini, druga komplikovana preeklampsijom. Tokom obe trudnoće koristila je metildopu, a nakon toga uvedena je stalna antihipertenzivna terapija – Nebilet plus. Tokom 2023. i 2024. godine imala je skokove krvnog pritiska (160/100 mmHg), praćene glavoboljom i stezanjem u grudima. Kontroliše se kod kardiologa koji joj je uveo beta-blokator, diuretik (indapamid) i blokator kalcijumskih kanala (amlodipin).

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Na ovoj terapiji pritisak joj je 80/65 mmHg. Početkom avgusta, CT abdomena je opisao uredne nadbubrežne žlezde. U ambulantnim uslovima sprovedeno je hormonsko ispitivanje, bez prethodnog wash-outa terapije, koje je pokazalo povišen noradrenalin (87; referentna vrednost do 79), dok su ostali hormoni bili u granicama normale. Ispitivanje RAAS osovine pokazuje renin u mirovanju 44 ng/ml, u naporu 68 ng/ml (referentno do 24), aldosteron u mirovanju 610 ng/ml, u naporu 236 ng/ml, uz ALDO/renin odnos 14, odnosno 11. Hipokalijemija nije registrovana. U jednom uzorku je povišen TSH (8,54; referentna vrednost do 4,85), ali nije uvedena L-T4 terapija. Glikoregulacija uredna (HbA1c 5,7%). Eho srca iz novembra 2023. godine pokazuje očuvanu ejekcionu frakciju (EF 66%), bez značajnih patoloških nalaza. Holter krvnog pritiska 24h pokazao je non-dipping obrazac sistolnog krvnog pritiska. Color Doppler sonografija vrata pokazuje početne ateroskleroske promene na ACI dex, kao i na arteriji subclaviae bilateralis. U ličnoj anamnezi drugih bolesti nema. Korektivna optička pomagala koristi od detinjstva. Majka leči krvni pritisak od njene 40. godine, otac ima stent na srcu. Bivši pušač.

Diskusija

Ključnu ulogu u regulaciji krvnog pritiska predstavlja renin-angiotenzin-aldosteron sistem (RAAS). Mehanizmi dejstva ostvaruju se preko angiotenzina i aldosterona, koji dovode do: aktivacije signala žeđi i autonomnog simpatičkog sistema, povećanja perifernog otpora i sužavanja glomerularnih arteriola uz reapsorpciju natrijuma i H_2O. Aktivacijom RAAS-a dolazi do posledičnog gubitka kalijuma i vodonikovih jona, što u uslovima poremećaja osovine može rezultirati metaboličkom acidozom, hipokalijemijom i hipertenzijom. Direktno ili indirektno na lučenje aldosterona utiču endogene i egzogene supstance: angiotenzin II, adrenokortikalni hormon (ACTH), hipokalijemija, ANP, beta-blokeri, diuretici, alfa-adrenergički agonisti. Shodno tome, neophodno je RAAS osovinu tumačiti na aldosteron-neutralnoj terapiji, te je neophodno zameniti antihipertenzivne lekove pre hormonskog ispitivanja: 4 do 6 nedelja za mineralokortikoidne antagoniste i diuretike koji štede kalijum i 2 nedelje za ostale lekove. Prema vodičima za aldosteronizam, alternativni antihipertenzivni lekovi su nedihidropiridinski blokatori kalcijumskih kanala i alfa-adrenergični blokatori. Pre uzorkovanja za renin i aldosteron, hipokalijemija mora da se koriguje supstitucijom u cilju prevazilaženja inhibitornog uticaja na lučenje aldosterona.

Primarna ili esencijalna hipertenzija se javlja kod većine pacijenata, dok 5 do 10% ima sekundarnu hipertenziju. Osim etiologije, glavna njihova razlika je u lečenju, budući da se pojedini uzroci sekundarnih hipertenzija mogu trajno izlečiti. Postavlja se pitanje kada uzeti u obzir moguće uzroke sekundarnih hipertenzija:

1. pojava hipertenzije u mladosti (oko 30 do 40 godina),
2. porodična anamneza sa ranom hipertenzijom i eventualnim kardiovaskularnim događajima,

3. teška hipertenzija sa dokazima organskih oštećenja,
4. rezistentna hipertenzija na 3 ili više antihipertenziva,
5. naglo pogoršanje ranije dobro kontrolisane hipertenzije,
6. hipertenzija povezana u kombinaciji sa opstruktivnom apnejom u snu.

Sa endokrinološkog aspekta, najčešći uzrok sekundarne hipertenzije je primarni aldosteronizam, a druge bolesti koje bi trebalo razmotriti su: feohromocitom, retke forme kongenitalne hiperplazije, hiperkortizolizam (Mb. Cushing, Cushing-ov sindrom, ektopični ACTH sindrom), tiroidna osovina (hipertireoza), akromegalija. Fizikalni pregled je standardizovan, ali se akcenat stavlja na merenje krvnog pritiska na obe ruke i na donjim ekstremitetima, opisivanje pulseva i auskultaciju eventualnih šumova u cilju isključivanja koarktacije aorte i mild aortnog sindroma. Takođe, RAAS osovina može biti narušena zbog renovaskularnih bolesti (ateroskleroza, fibromuskularna displazija, aneurizme, retroperitonealna fibroza, tumori) ili kod pacijenata sa jednim bubregom, što može pokrenuti sekundarni aldosteronizam. Lečenje se zasniva na primeni: A) ACE inhibitora i/ili blokatora angiotenzinskih receptora, sa važnom napomenom da kod obostranih stenoza primena oba leka može dovesti do akutne bubrežne insuficijencije, B) revaskularizaciji. Zlatni standard za postavljanje dijagnoze je arteriografija, kao i druge radiološke procedure poput dopler ultrazvuka, CT angiografije, MR angiografije i bubrežne scintigrafije.

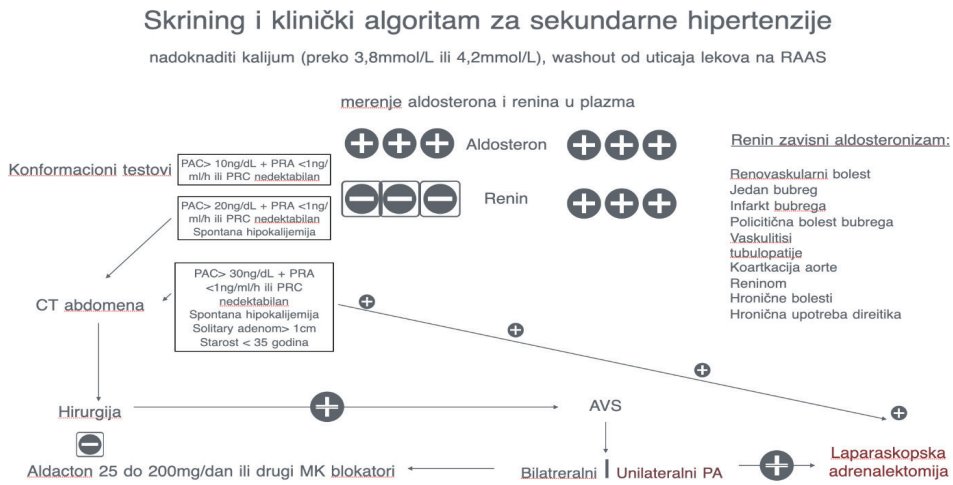
Druga bubrežna oboljenja, u čijoj etiopatogenezi je pokrenut vaskularni baroreceptorski mehanizam, a koja mogu dovesti do sekundarnog aldosteronizma, uključuju infarkt bubrega, vaskulitise (naročito poliarteritis nodozu) i policističnu bolest bubrega. Studijski podaci sugerišu da pacijenti sa koarktacijom aorte ili renovaskularnom hipertenzijom mogu imati normalne vrednosti aldosterona i renina, s obzirom na to da kod njih povišeni krvni pritisak može obnoviti bubrežnu perfuziju i tako maskirati hormonski sekundarni aldosteronizam. U medicinskoj praksi postoji redak entitet tumora jukstaglomerularnih ćelija – reninom, koji je uglavnom benigne prirode, a daje teške oblike hipertenzije sa izrazito povišenim reninom i aldosteronom. Dijagnoza se postavlja kateterizacijom bubrežnih vena, a izlečenje se postiže hirurškim putem. Postoje i drugi tumori koji mogu lučiti renin (ACC, hepatoblastom, Wilmsov tumor, leiomiomi materice).

Oblici sekundarnog aldosteronizma koji nisu praćeni hipertenzijom su Bartterov sindrom (mutacija Na-K-2Cl kotransportera sa simptomima: poliurija, hipovolemija, osteopenija, nefrokalcinoza, alkaloza i hipokalijemija) i Gitelmanov sindrom (mutacija Na-Cl transportera: hipokalijemija i hipomagnezijemija uz nisku kalcijurezu). Hronične bolesti, poput kongestivne srčane bolesti, ciroze jetre, nefrotskog sindroma i hronične upotrebe diuretika, dovode do morfoloških promena na nivou bubrega u smislu smanjenja broja funkcionalnih nefrona, a preostali, usled hiperfunkcije, postaju sklerotični uz smanjenu perfuziju i doprinose povećanom lučenju aldosterona. Na

kraju, sekundarni aldosteronizam predstavlja povećanje aldosterona kao odgovor na relativnu hipovolemiju, ali treba uzeti u obzir i primarni aldosteronizam, tj. Conn-ov sindrom, kod kojeg je produkcija aldosterona nezavisna od renina. Stoga je od ključnog značaja postaviti adekvatnu dijagnozu, budući da se terapijske opcije razlikuju kod ovih formi (shema 1).

Ključne stvari:

1. Sekundarni aldosteronizam karakterišu povišeni nivoi aldosterona i visoki ili nesupresovani nivoi renina.
2. Važno je prekinuti lekove koji utiču na sistem renin–angiotenzin–aldosteron najmanje 2–4 nedelje (u zavisnosti od leka, do 6 nedelja).
3. Potrebno je omogućiti slobodan unos soli (ad libitum) i obezbediti normokalemiju tokom dijagnostike.
4. Normalni nivoi aldosterona i renina ne isključuju sekundarni aldosteronizam – mogu biti maskirani volumenom.
5. Vaskularna stenoza (naročito renovaskularna) je glavni uzrok, ali postoje i oblici bez hipertenzije (npr. tubulopatije, hronične bolesti).
6. Merenje krvnog pritiska na donjim ekstremitetima je preporučeno kod sumnje na sekundarnu hipertenziju.



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*

Zaključak

Kod pacijentkinje sa arterijskom hipertenzijom, prisutnom od rane mladosti, postavljena je sumnja na sekundarne uzroke hipertenzije. Inicijalne vrednosti plazma renina i aldosterona ukazivale su na sekundarni aldosteronizam. Međutim, s obzirom na to da su analize sprovedene tokom terapije diureticima i pri pritiscima ranga hipotenzije, testiranje je ponovljeno nakon perioda prekida terapije (washout). Kontrolni nalazi pokazali su uredne koncentracije aldosterona (144.1 ng/L) i PRA (0,69ng/ml/h), što ukazuje na to da je prethodni disbalans RAAS osovine najverovatnije bio posledica relativne hipovolemije izazvane antihipertenzivnom terapijom, prvenstveno diureticima. U ovom kontekstu jedino ima smisla razmišljati o renovaskularnoj bolesti, s obzirom na aterosklerotske promene per anamnesis, ali tokom celokupnog perioda washout-a krvni pritisak je ostao stabilan, uz uredne druge biohemijske parametre, što dodatno podržava ovu pretpostavku i praktično isključuje druge uzroke renin-zavisnog aldosteronizma.

Literatura

1. Young WF Jr. Diagnosis and management of primary aldosteronism. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000– [updated 2018 Feb 8; cited 2024 Dec 6].
2. Scott JH, Menouar MA, Dunn RJ. Physiology, Aldosterone. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan– [updated 2023 May 1]. PMID: 29261963.
3. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016; 101(5): 1889–916. doi:10.1210/jc.2015-4061. PMID: 26934393.
4. Hellman P, Björklund P, Åkerström T. Aldosterone-producing adenomas. *Vitam Horm.* 2019; 109:407–31. doi:10.1016/bs.vh.2018.10.007. PMID: 30678866.
5. Wagner CA. Effect of mineralocorticoids on acid-base balance. *Nephron Physiol.* 2014; 128(1–2): 26–34. doi:10.1159/000368266. PMID: 25377117.
6. Schilbach K, Junnila RK, Bidlingmaier M. Aldosterone to renin ratio as screening tool in primary aldosteronism. *Exp Clin Endocrinol Diabetes.* 2019; 127(2–3): 84–92. doi-:10.1055/a-0672-0836. PMID: 30165708.
7. Cruz DN, Perazella MA. Hypertension and hypokalemia: unusual syndromes. *Conn Med.* 1997; 61(2): 67–75. PMID: 9066195.
8. Gruber S, Beuschlein F. Hypokalemia and the prevalence of primary aldosteronism. *Horm Metab Res.*2020; 52(6): 347–56. doi:10.1055/a-1134-4980. PMID: 32252108.
9. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the

Eighth Joint National Committee (JNC 8). *JAMA*. 2014; 311(5): 507–20. doi:10.1001/jama.2013.284427.

10. Gordon RD, Stowasser M, Klemm SA, Tunny TJ. Primary aldosteronism and other forms of mineralocorticoid hypertension. In: Swales JD, editor. *Textbook of Hypertension.* London: Blackwell Scientific Publications; 1994. pp. 865–92.
11. Kaplan NM. Primary aldosteronism. In: Kaplan NM, editor. *Kaplan's Clinical Hypertension.* 8th ed. New York: Lippincott Williams and Wilkins; 2002. pp. 455–79.
12. McAlister FA, Lewanczuk RZ. Primary hyperaldosteronism and adrenal incidentaloma: an argument for physiologic testing before adrenalectomy. *Can J Surg.* 1998; 41(4): 299–305. PMID: 9711163; PMCID: PMC3950085.
13. Faconti L, Kulkarni S, Delles C, et al. Diagnosis and management of primary hyperaldosteronism in patients with hypertension: a practical approach endorsed by the British and Irish Hypertension Society. *J Hum Hypertens.* 2024; 38(1): 8–18. doi:10.1038/s41371-023-00875-1.
14. Solar M, Makarova E, Ballon M, Pelouch R, Ceral J. Confirmatory testing in primary aldosteronism: extensive medication switching is not needed in all patients. *Eur J Endocrinol.* 2012; 166(4): 679–86. doi:10.1530/EJE-11-0914. PMID: 22253400; PMCID: PMC3315831.
15. Rossi GP, Belfiore A, Bernini G, Desideri G, Fabris B, Ferri C, et al. Comparison of the captopril and the saline infusion test for excluding aldosterone-producing adenoma. *Hypertension.* 2007; 50(3): 424–31.
16. Young WF Jr. Diagnosis and management of primary aldosteronism. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. *Endotext*. South Dartmouth (MA): MDText.com, Inc.; 2000–. Updated 2018 Feb 8. PMID: 25905209.
17. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2016; 101(5): 1889–916. PMID: 26934393.

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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:

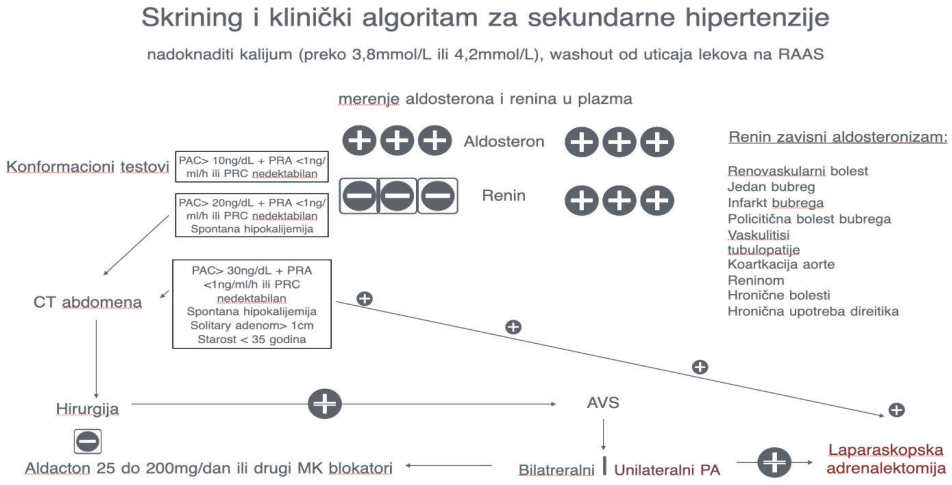
1. Early-onset hypertension (age 30–40)
2. Family history of early-onset hypertension or cardiovascular events
3. Severe hypertension with organ damage
4. Resistant hypertension to 3+ drugs
5. Sudden worsening of previously well-controlled hypertension
6. Hypertension associated with obstructive sleep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



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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.

References

1. Young WF Jr. Diagnosis and management of primary aldosteronism. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000– [updated 2018 Feb 8; cited 2024 Dec 6].
2. Scott JH, Menouar MA, Dunn RJ. Physiology, Aldosterone. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan– [updated 2023 May 1]. PMID: 29261963.
3. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016; 101(5): 1889–916. doi:10.1210/jc.2015-4061. PMID: 26934393.
4. Hellman P, Björklund P, Åkerström T. Aldosterone-producing adenomas. *Vitam Horm.* 2019; 109:407–31. doi:10.1016/bs.vh.2018.10.007. PMID: 30678866.
5. Wagner CA. Effect of mineralocorticoids on acid-base balance. *Nephron Physiol.* 2014; 128(1–2): 26–34. doi:10.1159/000368266. PMID: 25377117.
6. Schilbach K, Junnila RK, Bidlingmaier M. Aldosterone to renin ratio as screening tool in primary aldosteronism. *Exp Clin Endocrinol Diabetes.* 2019; 127(2–3): 84–92. doi-:10.1055/a-0672-0836. PMID: 30165708.
7. Cruz DN, Perazella MA. Hypertension and hypokalemia: unusual syndromes. *Conn Med.* 1997; 61(2): 67–75. PMID: 9066195.
8. Gruber S, Beuschlein F. Hypokalemia and the prevalence of primary aldosteronism. *Horm Metab Res.*2020; 52(6): 347–56. doi:10.1055/a-1134-4980. PMID: 32252108.
9. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA.* 2014; 311(5): 507–20. doi:10.1001/jama.2013.284427.
10. Gordon RD, Stowasser M, Klemm SA, Tunny TJ. Primary aldosteronism and other forms of mineralocorticoid hypertension. In: Swales JD, editor. *Textbook of Hypertension.* London: Blackwell Scientific Publications; 1994. pp. 865–92.
11. Kaplan NM. Primary aldosteronism. In: Kaplan NM, editor. *Kaplan's Clinical Hypertension.* 8th ed. New York: Lippincott Williams and Wilkins; 2002. pp. 455–79.
12. McAlister FA, Lewanczuk RZ. Primary hyperaldosteronism and adrenal incidentaloma: an argument for physiologic testing before adrenalectomy. *Can J Surg.* 1998; 41(4): 299–305. PMID: 9711163; PMCID: PMC3950085.

13. Faconti L, Kulkarni S, Delles C, et al. Diagnosis and management of primary hyperaldosteronism in patients with hypertension: a practical approach endorsed by the British and Irish Hypertension Society. *J Hum Hypertens.* 2024; 38(1): 8–18. doi:10.1038/s41371-023-00875-1.
14. Solar M, Makarova E, Ballon M, Pelouch R, Ceral J. Confirmatory testing in primary aldosteronism: extensive medication switching is not needed in all patients. *Eur J Endocrinol.* 2012; 166(4): 679–86. doi:10.1530/EJE-11-0914. PMID: 22253400; PMCID: PMC3315831.
15. Rossi GP, Belfiore A, Bernini G, Desideri G, Fabris B, Ferri C, et al. Comparison of the captopril and the saline infusion test for excluding aldosterone-producing adenoma. *Hypertension.* 2007; 50(3): 424–31.
16. Young WF Jr. Diagnosis and management of primary aldosteronism. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. *Endotext*. South Dartmouth (MA): MDText.com, Inc.; 2000–. Updated 2018 Feb 8. PMID: 25905209.
17. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2016; 101(5): 1889–916. PMID: 26934393.