CLINICAL VIGNETTE

Hypokalemic Hyperaldosteronism with Unilateral Adrenal Adenoma

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Introduction

The hypersecretion of aldosterone with primary aldosteronism (PA) was once an underdiagnosed cause of secondary hypertension that now may be one of the most frequent causes. It was previously thought to involve less than 1% of hypertensive patients, particularly those with hypokalemia. However, recent studies have shown that hypokalemia is variably present in patients with PA (9 to 37%).[1] With the increased use of the plasma aldosterone concentration to plasma renin activity ratio (PAC/PRA) as a screening test in both hypokalemic and normokalemic patients with uncontrolled or resistant hypertension, increasing prevalence has been in the last 15 years.[2]

Case

A 51-year-old male initially presented to his Cardiologist for blood pressure management. Hypertension was diagnosed many years ago. His past medical history also included mild obstructive sleep apnea, hyperlipidemia, hypertension, and mild peripheral arterial disease noted on CT coronary calcium scan. Medications included amlodipine 5mg twice daily and ramipril 10 mg twice daily. On this regimen, his home systolic blood pressure was averaging 150. He also reported use of a nitric oxide supplement, which allowed him to reduce his systolic blood pressure to the 130 to 150 range. He exercises for 60 minutes on a treadmill 4 to 5 days a week and denies any chest pain, shortness of breath, or palpitation with exertion. His family history is notable for coronary artery disease diagnosed in his father in his 20's. His mother has severe hypertension. Although he was previously diagnosed with obstructive sleep apnea he chose not to use a CPAP machine.

A Cardiologist's appointment, his blood pressure was 138/89. Office EKG revealed sinus bradycardia with heart rate of 55 bpm, Q waves in V1 and V2 and left ventricular hypertrophy. His medication regimen was changed to amlodipine 10 mg once nightly and irbesartan 150 mg once daily. Potassium level was 3.0 mmol/L and creatinine was 1.02 mg/dl. Potassium increased to 3.3 after supplementation.

After one month, despite medication compliance, home systolic blood pressures ranged from 130 to 150. Irbesartan was increased to 300 mg once daily and eplerenone 25 mg once nightly was started. Home systolic blood pressure measurements remained elevated in the 150 to 160 range. The eplerenone was increased to 50 mg nightly and labetalol 100 mg twice daily was added. Due to cost issues, irbesartan was switched to losartan 100 mg once daily.

He was referred to Nephrology, who initiated further evaluation for secondary hypertension including tests for renin, aldosterone, serum metanephrines, and renal doppler ultrasound. The workup was significant for the plasma aldosterone concentration to plasma renin activity ratio (PAC/PRA) of 19.2/0.1 or 50. Repeat testing confirmed a PAC/PRA ratio of 26/0.2 or 50. This is suggestive of primary hyperaldosteronism. A CT scan of the adrenal glands with and without contrast showed a 12 mm left adrenal nodule with enhancement pattern consistent with likely adenoma. The contralateral adrenal gland was normal in size and morphology with no mass. He was referred to Endocrine Surgery. At this time, he noted fatigue, palpitations, and weight gain. He continued to deny any chest pain, shortness of breath, dizziness, headaches. He also discontinued potassium supplementation, labetalol, and losartan due to intolerance. A left retroperitoneoscopic adrenalectomy was performed, with pathology suggesting a benign adrenal cortical adenoma, with Modified Weiss Criteria of 2. A score greater than 3 would indicate malignant behavior.

After the surgery, his blood pressure improved to approximately 120/70 while on amlodipine 5mg once daily and hypokalemia resolved. Months after surgery, his blood pressure remains at goal while on amlodipine.

Discussion

Primary aldosteronism promotes volume expansion and a potential increase in systemic vascular resistance, which promotes hypertension. It also suppresses renin release, leading to a decrease in renin concentration and activity. This is unlike other secondary causes of hyperaldosteronism such as renovascular hypertension, aortic coarctation or diuretic therapy. Aldosterone increases the number of open sodium channels (epithelial sodium channel or ENaC) in the luminal membrane of the principal cells within the renal collecting duct. Sodium reabsorption then increases, which leads to the secretion of cellular potassium into the lumen through potassium channels (ROMK) in the luminal membrane. Excess aldosterone leads to potassium-wasting, which can be counterbalanced by a potassium-retaining effect from hypokalemia. Urinary potassium wasting can also occur. The loss of potassium can increase with decreased intake or diuretic use, particularly those acting

proximal to the potassium secreting site such as thiazide and loop diuretics.[3]

Diagnostic testing can be considered for those with uncontrolled hypertension involving 3 separate readings greater than 150/100, persistent hypertension despite the use of 3 blood pressure medications, including a diuretic, and the need for at least 4 blood pressure medications to maintain levels less than 140/90. Other considerations included diuretic-induced hypokalemia, hypertension with adrenal incidentaloma, hypertension with sleep apnea, hypertension with a family history of early-onset hypertension or cerebrovascular accident at a young age, less than 40.[4]

The initial screening test for primary aldosteronism measures plasma aldosterone concentration to plasma renin activity ratio (PAC/PRA). Testing for PAC and PRA is done in the morning after the patient has been awake for at least 2 hours. The patient should be in a seated position for 5 to 15 minutes. Restricting dietary salt intake prior to testing is not advised. Aldosterone secretion increases when standing and with decreasing sodium intake while renin levels are increased by decreases in sodium intake and standing.[5] Ideally, hypokalemia is corrected prior to testing.

Based on a systematic literature review by Montori et al, there are variations in the aldosterone to renin ratio cut-off values for fulfilling the diagnosis, ranging from 7.2 to 100 ng/dl per ng/ml.[6] The variation limits diagnostic accuracy.

Other considerations include the anti-hypertensive medication regimen. Mulatero et al concluded that α-blockers and ACE-inhibitors can be used in patients for whom anti-hypertensive treatment cannot be stopped as they do not interfere significantly with diagnosis. One small study reported a high rate of false-negative diagnoses in patients taking irbesartan. This study showed amlodipine use had a low percentage of false-negative diagnoses. β-Blockers were associated with increased false-positive ratios.[7] Given the potential for medication interference, they can be held for at least 2 weeks prior to testing. Mineralocorticoid receptor antagonists and potassium-wasting diuretics also markedly affected the ratio. It is recommended to hold these medications for at least 4 weeks prior to testing. If there is concern for hypertension control during that time, patients can be switched to other medications that have less impact on the ratio including verapamil slow-release, hydralazine or α-blockers.[4]

If the ratio is elevated and there is concern for false positive results, the next step involves confirmatory suppression tests, such as oral sodium loading or intravenous saline infusion. However, in the setting of spontaneous hypokalemia, plasma renin below detection levels and plasma aldosterone concentration (PAC) of 20 ng/dl, further confirmatory testing may not be needed. Oral sodium loading involves a high sodium diet > 200mmol/day for 3 days. With 24-h urine aldosterone, sodium and creatinine collection on day 3. Urinary aldosterone excretion more than 12 µg/24 h is consistent with autonomous aldosterone secretion. The intravenous saline infusion test is performed after an overnight fast. 2 liters of 0.9% sodium chloride solution is infused over 4 hours into the recumbent patient, after which PAC is measured. Primary aldosteronism is suspected if plasma aldosterone is greater than 10 ng/dl.[4]

Once primary hyperaldosteronism has been confirmed, CT of the adrenal glands with contrast is advised to determine the presence of an adenoma. Laparoscopic adrenalectomy is considered if a solitary, unilateral macroadenoma between 1 to 2 cm is detected. This procedure has reported morbidity between 5 and 14% and mortality of less than 1%.[8] Adrenal carcinoma is suspected with a unilateral adrenal mass measuring at least 4 cm. Bilateral adrenal gland thickening suggests adrenal hyperplasia. Once surgery is considered, subtype differentiation with adrenal venous sampling (AVS) can determine whether aldosterone hypersecretion is unilateral or bilateral. This is an invasive procedure that determines aldosterone and cortisol levels in the inferior vena cava and in the two adrenal veins. Younger patients, less than age 35 years with spontaneous hypokalemia, marked aldosterone excess, and a confirmed adenoma may not need AVS due to a higher probability of unilateral disease.[9]

Post-procedure normalization of aldosterone secretion and hypokalemia is more frequent in young patients with recent hypertension than in patients with long-standing hypertension or a family history of hypertension.[5] Therefore, anti-hypertensive medication may still be advised, as seen in this case. Patients who are not able to undergo surgery or have bilateral adrenal disease are treated with a mineralocorticoid receptor antagonist.

Conclusion

The benefits of pursuing diagnosis and treatment of primary aldosteronism in the early stages include the prevention of morbidity and mortality associated with hypertension and reducing cardiovascular risk from stroke, myocardial infarction, heart failure, and atrial fibrillation. This applies to patients with aldosterone-producing adenoma or bilateral adrenal hyperplasia. Primary aldosteronism has also been associated with increased risk of diabetes, metabolic syndrome and left ventricular hypertrophy. Cardiovascular risk should resolve with treatment.[10]

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