

CLINICAL VIGNETTE

Hypertension and Hypokalemia

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A 47-year-old African-American woman was noted to be hypokalemic on exam prior to knee surgery. She has a history of rheumatoid arthritis and hypertension and she had been on hydrochlorothiazide and potassium chloride. Her follow-up potassium levels showed persistent hypokalemia despite increasing potassium supplementation and discontinuing diuretics. She denied vomiting, diarrhea, licorice intake or laxative use. She noted fatigue and a 15 pound weight gain over the past 18 months. Aldosterone level was elevated at 18 with suppressed plasma renin activity of 0.1 ng/mL/hr and cortisol normal. Her antihypertensives were changed to nisoldipine and labetalol and her systolic blood pressures on this regimen ranged from 140 to 160s.

Family history was positive for coronary disease and prostate cancer in her father and bladder cancer in her mother.

Her physical exam was normal except for a systolic blood pressure of 160.

Abdominal ultrasound showed no renal artery stenosis. MRI of the abdomen revealed a right adrenal nodule and a saline load test confirmed the diagnosis of primary hyperaldosteronism.

The patient underwent laparoscopic adrenalectomy, and postoperatively, her aldosterone level decreased to 1.4. Her hypokalemia resolved and her blood pressure was controlled with labetalol and amlodipine.

Hyperaldosteronism

Primary aldosteronism is the most common form of secondary hypertension with an estimated prevalence of 5%-13% of all patients with hypertension¹. In 1954, Dr. Jerome Conn presented a case of a young woman with hypertension, severe hypokalemia and elevated

levels of mineralocorticoid. During surgery, she was found to have an adrenal tumor. After removal of the involved adrenal gland, her laboratory abnormalities and hypertension resolved². In addition to aldosterone-producing adenomas described by Conn, other causes of primary aldosteronism include bilateral adrenal hyperplasia, adrenocortical carcinomas, familial hyperaldosteronism type 1 (glucocorticoid-remediable aldosteronism) and type II and ectopic aldosterone-producing tumors³. Thirty-five percent of cases are due to aldosterone-producing adenomas, 60% from bilateral adrenal hyperplasia and the remaining 5% of cases of primary aldosteronism are due to familial hyperaldosteronism, adrenocortical carcinomas, and ectopic aldosterone-producing tumors.

Other causes of hypertension and hypokalemia include Cushing's syndrome, licorice ingestion, renin-secreting tumors, and Liddle's syndrome⁴.

There are few clinical features specific to primary aldosteronism. Elevated aldosterone levels cause increased sodium reabsorption and hypervolemia. Hypervolemia can cause moderate to severe hypertension refractory to medications¹. However, sodium retention does not cause edema because of counteractive responses to the hypervolemia. Increased atrial natriuretic peptide and enhanced sodium excretion at the kidneys in response to hypervolemia causes a spontaneous diuresis⁵. Hypokalemia is present due to potassium excretion, but due to potassium-retaining effects of the kidneys in response to hypokalemia, patients can be normokalemic in a steady state until diuretics are used or when there is increased aldosterone production. Severe hypokalemia can lead to muscle weakness and cramps, headaches, palpitations, polyuria and nocturia. The elevated aldosterone level suppresses renin levels which distinguishes

hypertension due to primary aldosteronism from hypertension due to renovascular or malignant hypertension or renin-secreting tumor⁴.

Hyperaldosteronism has been shown to have serious clinical consequences. Vasani followed nonhypertensive participants from the community for four years to study the relationship of aldosterone levels and incidence of hypertension. Higher levels of aldosterone, even within the physiologic range, correlated with increased blood pressure and the highest elevation of aldosterone showed a 1.6 fold risk of hypertension compared to the lowest levels of aldosterone measurements⁶. A study by Milliez noted a higher incidence of strokes (12.9% vs 3.4%), myocardial infarction (4.0% vs 0.6%) and atrial fibrillation (7.3% vs. 0.6%) in patients with primary aldosteronism versus patients with essential hypertension⁷. Patients with primary aldosteronism also developed higher left ventricular mass than patients with other types of hypertension. Patients also had increased carotid arterial wall thickness and higher urinary albumin excretion than patients with essential hypertension⁸.

Due to the increased cardiovascular complications associated with hyperaldosteronism, guidelines have been established to identify patients with primary hyperaldosteronism. According to recommendations of The Endocrine Society Clinical Practice Guideline, patients eligible for screening “include patients with Joint National Commission stage 2 (>160-179/100-109 mm Hg), stage 3 (>180/110 mm Hg), or drug-resistant hypertension; hypertension and spontaneous or diuretic-induced hypokalemia; hypertension with adrenal incidentaloma; or hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 yr).” All hypertensive patients with first-degree relatives who have primary aldosteronism should also be screened⁹.

The random plasma aldosterone to plasma renin ratio is used for screening. The plasma aldosterone-renin ratio was traditionally done after discontinuing antihypertensives but a

prospective study by Gallay et al. demonstrated that discontinuing antihypertensives except for spironolactone was not necessary¹⁰. The Endocrine Society Clinical Practice Guideline recommends collection of samples in the morning after patients have been out of bed for at least 2 hours and after being seated for 5-15 minutes. Patients are able to eat an unrestricted salt diet before the test and most antihypertensives can be continued except spironolactone, eplerenone, amiloride, and triamterene, which should be discontinued for 4 weeks prior to screening. Patients also should avoid licorice and chewing tobacco. Other medications such as verapamil, prazosin, terazosin, doxazosin and hydralazine can be used to substitute for medications that were discontinued for blood pressure control. Due to variability in laboratories and assay methods, there is a range of cutoff values for a positive test. Therefore, the diagnosis should be confirmed with aldosterone suppression testing to show inappropriate aldosterone secretion⁹. The test can be done either with oral sodium chloride followed by measurement of urinary aldosterone excretion or with parenteral sodium chloride loading and measurement of plasma aldosterone concentration¹. The 2008 Endocrine Society Guidelines also have the fludrocortisone suppression or captopril challenge test as additional confirmatory testing methods⁹.

After confirmatory tests have confirmed the diagnosis of primary aldosteronism, adrenal CT scan can assist in identifying adrenal adenomas versus bilateral adrenal hyperplasia or adrenal carcinoma. However adrenal CT scans have limitations in identifying a functional versus nonfunctional nodule or visualizing microadenomas. Adrenal vein sampling (AVS) can be used in conjunction with adrenal CT to distinguish between unilateral versus bilateral disease in patients who are contemplating surgery. Many centers use continuous cosyntropin infusion during AVS to maximize the secretion of aldosterone from an adrenal nodule and maximize the gradient of cortisol from the adrenal vein to the inferior vena cava to confirm accurate sampling of the adrenal vein and to minimize stress-induced fluctuations in

aldosterone secretion during sequential adrenal vein sampling⁹.

For patients with primary aldosteronism who are younger than 20 years old or who have a family history of primary aldosteronism or strokes at a young age, genetic testing should be done to assess for familial hyperaldosteronism⁹.

In a retrospective study by Blumenfeld, 35% of patients with adenoma achieved cure of hypertension with surgery alone. These patients tended to be younger and have lower pretreatment renin levels¹¹. Patients who had persistent hypertension were older, were taking more than two antihypertensive medications preoperatively, had increased creatinine level, longer duration of hypertension and more than one first-degree relative with hypertension¹. For patients with bilateral adrenal hyperplasia, glucocorticoid-remediable aldosteronism, or who do not want surgery, spironolactone or eplerenone are used. In a prospective study by Catena, patients with primary aldosteronism were followed after adrenalectomy or spironolactone therapy. The study found that at baseline, cardiovascular events such as myocardial infarction, stroke, arrhythmias, and revascularization procedures were more prevalent in the primary aldosteronism group than in the essential hypertension group. However after treatment, the rates of cardiovascular events were similar for both groups¹².

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