CHALK TALK

Seeing is Believing—Just not in Primary Aldosteronism

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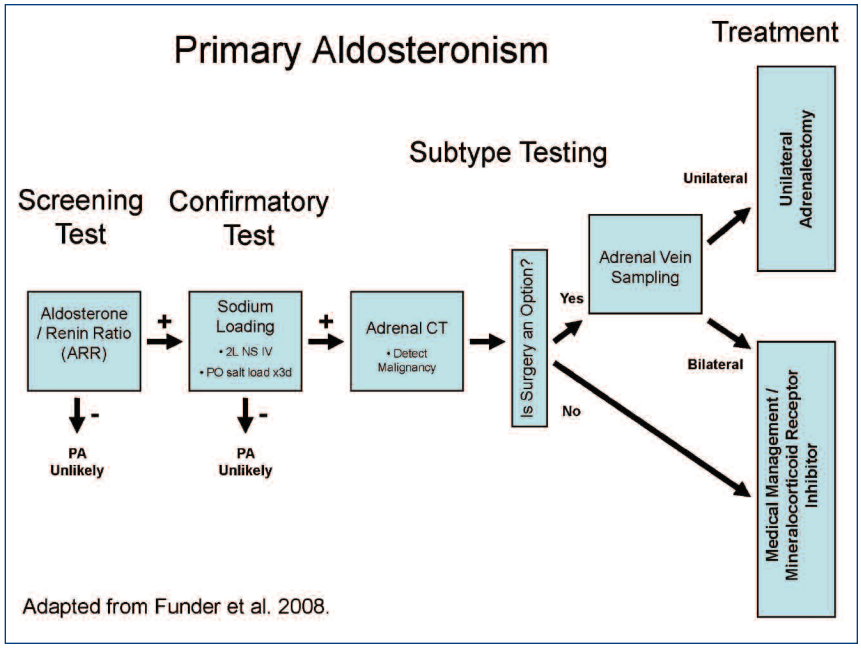
Objective: To provide a framework for the evaluation and treatment of primary aldosteronism

Case: A 52-year-old man with hypertension, metabolic alkalosis, and hypokalemia has poorly controlled blood pressure despite treatment with four antihypertensive agents. In addition, he was incidentally found to have a 1.2 cm left adrenal adenoma during work-up of abdominal pain that has since resolved. How should he be evaluated for possible primary hyperaldosteronism? If primary aldosteronism is confirmed, should he just undergo left adrenalectomy, or should adrenal vein sampling be performed before surgical intervention?

Teaching goal: To convey the normal physiology of aldosterone regulation and the evaluation and treatment of primary aldosteronism

Aldosterone Physiology: Under normal circumstances, aldosterone secretion from the adrenal gland is regulated by both the renin-angiotensin system and the extracellular potassium (K^+) concentration. A drop in renal perfusion pressure stimulates the release of renin into the circulation, which results in the conversion of angiotensinogen to angiotensin II through a number of enzymatic steps. Activation of the angiotensin II receptor in the adrenal gland promotes the synthesis and secretion of aldosterone from the adrenal cortex. Aldosterone is also the primary regulator of K^+ concentration in the body. High circulating K^+ levels cause membrane depolarization of the zona glomerulosa and directly trigger aldosterone secretion, whereas a low K^+ concentration has the opposite effect.



The physiologic effects of aldosterone are primarily mediated by its actions on the principal and intercalated cells of the distal nephron. In these cells, aldosterone increases the expression and activity of the basolateral Na-K-ATPase as well as the luminal Na^+ epithelial channels (ENaC) and hydrogen pumps to give rise to Na^+ retention, K^+ loss, and H^+ excretion, resulting in increased blood pressure, decreased plasma K^+, and metabolic alkalosis, \respectively.

Primary Aldosteronism: Primary aldosteronism refers to a group of disorders in which aldosterone production is inappropriately elevated, not regulated by the renin-angiotensin system, and not suppressible by sodium loading. Primary aldosteronism is a common cause of secondary hypertension, occurring in approximately 5% of all hypertensive patients.

Case Detection: The prevalence of primary aldosteronism increases significantly among patients who have severe hypertension and those on more than three antihypertensive agents. These patients should be screened for possible primary aldosteronism. In addition, screening is recommended in patients with hypertension and hypokalemia (spontaneous or diuretic induced), hypertensive patients with adrenal incidentalomas, young patients with hypertension, and hypertensive patients with a family history of stroke prior to age 40. It is important to note that hypokalemia is found in less than 50% of patients with primary aldosteronism, so normal K^+ levels cannot be used to exclude this diagnosis.

Screening Tests: The initial screening for primary aldosteronism involves the morning ambulatory measurement of plasma aldosterone concentration (PAC) and concurrent plasma renin activity (PRA) to calcu-

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late the aldosterone to renin ratio (ARR). Patients can continue on their antihypertensive agents except for spironolactone, eplerenone, amilioride, and triamterene, which significantly interfere with the interpretation of test results. Verapamil, hydralazine, and alpha blockers are the preferred agents as they have minimal impact on screening tests. Other blood pressure agents can slightly decrease the sensitivity or specificity of the measurements but to an acceptable degree.

A positive screen occurs when the both the aldosterone (ng/dL) to renin (ng/mL/h) ratio (ARR) is greater than 20 *and* the aldosterone concentration is greater than 10 to 15 ng/dL. An important caveat is that the assays are not standardized, so cutoff values are dependent on the specific assays used. In general, as the ARR and the PAC increase, the specificity of the screen increases and the sensitivity decreases.

Confirmatory Test: Because of limitations with the specificity of the screening test, a positive result requires confirmatory testing. As with most endocrine disorders involving a hypersecretory state, confirmatory testing for hyperaldosteronism involves an attempt to suppress hormone secretion. This is accomplished by driving down renin production with a sodium load. Under normal circumstances, the volume expansion resulting from a sodium load should suppress renin and aldosterone levels. Failure to suppress aldosterone secretion confirms the presence of primary aldosteronism.

Sodium loading is commonly accomplished by one of two methods. The first involves the infusion of 2 liters of normal saline over a 4-hour time period. If plasma aldosterone levels are not suppressed at the end of the infusion (PAC > 10 ng/dL), primary aldosteronism is confirmed. Alternatively, patients can be instructed to increase dietary sodium intake to approximately 6 grams per day for 3 days. On the third day, a 24-hour urine collection is obtained for measuring urinary sodium and aldosterone. Urinary sodium measurements of more than 200 mEq ensures adequate salt loading, and urinary aldosterone levels greater than 12 µg confirm the diagnosis of primary aldosteronism. It is important to avoid hypokalemia during the salt load as this can decrease the sensitivity of the test.

Subtypes: After primary aldosteronism has been confirmed, the next step is to determine the cause. Different subtypes of primary aldosteronism vary in both their treatment modalities and relative frequencies. Bilateral etiologies require medical management whereas unilateral causes are amenable to surgical treatment. The bilateral causes include bilateral adrenal hyperplasia, also known as idiopathic hyperaldosteronism, and familial hyperaldosteronism. Unilateral subtypes include aldosterone producing adenomas and carcinomas and unilateral adrenal hyperplasia. The most common cause of primary aldosteronism is bilateral adrenal hyperplasia, which accounts for almost two thirds of cases. The second most common etiology is an aldosterone producing adenoma, occurring in approximately 30% of individuals with primary aldosteronism. The other causes account for less than 5% of cases, with unilateral adrenal hyperplasia accounting for the majority of the relatively rare causes. However, because ~1% of cases of hyperaldosteronism are caused by adrenal cancer, adrenal CT is recommended in all patients.

Surgical vs. Medical Management: As true differentiation between unilateral and bilateral disease requires an invasive procedure, the next step after cancer has been ruled out by adrenal imaging is to determine whether the patient is a surgical candidate. When clinical features or personal preferences exclude unilateral adrenalectomy as an option, medical treatment can be initiated without further evaluation. If, on the other hand, the patient is willing to consider possible definitive therapy, additional testing is required to determine if the primary aldosteronism is caused by unilateral or bilateral disease.

Only unilateral disease, like aldosterone producing adenomas and unilateral hyperplasia, responds to unilateral adrenalectomy. Bilateral disease, which accounts for approximately two thirds of cases, requires medical management. Treatment with either of the mineralocorticoid receptor blockers, spironolactone or eplerenone, significantly improves blood pressure and normalizes hypokalemia in the majority of patients with primary aldosteronism.

Although hypertension and hypokalemia tend to be more severe in patients with aldosterone-producing adenoma than bilateral adrenal hyperplasia, clinical markers have poor discriminatory function due to the large degree of overlap. Likewise, the radiographic appearance of the adrenal glands correlates poorly with the functional hyperaldosteronism. Recent studies have convincingly shown that 1) the presence of an adrenal nodule in a patient with primary aldosteronism does not prove the diagnosis of an aldosterone-producing adenoma, and 2) its absence does not exclude unilateral disease. This is because non-functioning adrenal adenomas are common, the

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adrenal glands in bilateral adrenal hyperplasia may have nodular changes, and unilateral disease may result in normal-appearing adrenal glands.

Adrenal Vein Sampling: The definitive test for distinguishing unilateral (surgical treatment) from bilateral causes (medical treatment) is adrenal vein sampling. By catheterizing the right and left adrenal veins and comparing cortisol-corrected aldosterone ratios between the two adrenal glands and the periphery, one can determine with a high degree of confidence whether the hyperaldosteronism lateralizes to either the left or right adrenal gland or whether it is caused by bilateral disease.

When compared to adrenal CT, adrenal vein sampling better identifies the source of unilateral disease and determines which patients have bilateral adrenal hyperplasia. In fact, adrenal CT was accurate in identifying the source of the hyperaldosteronism in only about half the patients with primary aldosteronism compared to adrenal venous sampling. Relying on the imaging findings alone would have resulted in about a quarter of patients undergoing unnecessary surgery and another quarter being incorrectly excluded from potentially curative adrenalectomies.

Resolution of Case: Screening for primary aldosteronism was positive with a PAC of 28 ng/dL and a PRA of < 0.6 ng/mL/h, yielding an aldosterone to renin ratio (ARR) > 47. IV saline load confirmed the diagnosis of primary aldosteronism with failure to suppress aldosterone levels (16 ng/dL). Despite the presence of a left adrenal nodule, adrenal vein sampling showed elevated aldosterone secretion from both adrenal glands without evidence of lateralization. The test results indicated that the patient had a non-functional adrenal adenoma, which has a prevalence of about 4% among patients in their sixth decade, and bilateral adrenal hyperplasia. Treatment with spironolactone normalized hypokalemia and gradually improved blood pressure control so he was able to discontinue all other antihypertensive agents.

References

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