SEMINARS IN
NEPHROLOGY

Mineralocorticoid Hypertension and Hypokalemia

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Mineralocorticoid hypertension is hypertension associated with the presence of hypokalemia, metabolic alkalosis, and suppression of plasma renin. Mineralocorticoid hypertension represents only 10% of patients with essential hypertension. However, its recognition is important because it is a potentially reversible cause of hypertension. Primary hyperaldosteronism is the most common form of mineralocorticoid hypertension. It is current clinical practice to use the plasma aldosterone-renin ratio and the absolute plasma aldosterone level as screening tests. Confirmatory suppression tests and adrenal imaging are performed in appropriate patients. Three monogenic forms of mineralocorticoid hypertension have been identified including Liddle's syndrome, glucocorticoid-remediable hypertension, and apparent mineralocorticoid excess. In a number of patients with mineralocorticoid hypertension, hypokalemia can be a variable finding. This review highlights mineralocorticoid biology and important features of primary hyperaldosteronism and monogenic hypertension.
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Mineralocorticoid hypertension is a potentially reversible cause of hypertension that is characterized by the triad of hypertension, metabolic alkalosis, and hypokalemia. It refers to hypertension that is caused by increased retention of sodium by the nephron, expansion of the extracellular fluid compartment, and suppression of plasma renin. Of note, edema is not often present because of the sodium-escape phenomenon and normokalemia may be present in some forms of mineralocorticoid hypertension.[1] The potential causes of mineralocorticoid hypertension are presented in Table 1.

The true incidence of mineralocorticoid hypertension in an unselected community-based population is unclear and screening remains a widely debated topic. Certainly it is clear that all hypertensive patients should have their electrolyte levels checked and further testing should be performed if unprovoked hypokalemia is present. Screening of patients with difficult-to-control hypertension, rapid onset of disease, and possibly a strong family history of early onset hypertension and cerebrovascular disease is advisable.

This review discusses the biology of aldosterone followed by a discussion of primary hyperaldosteronism, the most common form of mineralocorticoid hypertension. It also discusses 2 monogenic forms of this class of hypertension: glucocorticoid-remediable hyperaldosteronism (GRA) and apparent mineralocorticoid excess (AME). Additional differential diagnoses also are highlighted, including abnormalities seen in essential hypertension that have been discovered from our understanding of monogenic forms of hypertension.

Mineralocorticoid Secretion and Hormone Action

An understanding of mineralocorticoid hypertension requires an understanding of aldosterone biosynthesis, regulation, and action. The major adrenal hormones are synthesized in different compartments of the adrenal cortex: aldosterone in the zona glomerulosa and glucocorticoids in the zona fasiciculata. Angiotensin II and increased potassium levels primarily regulate aldosterone secretion. Its synthesis requires 11-β hydroxylation followed by zona glomerulosa–specific 18 hydroxylation and 18 oxidation of deoxycorticosterone.[2-5] These latter 2 reactions are mediated by a single,

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Table 1 Differential Diagnosis of Mineralocorticoid Hypertension

Diagnosis based on responsible mineralocorticoid
Aldosterone
Adrenal adenoma
Bilateral adrenal hyperplasia
Adrenal carcinoma
GRA
Cortisol via 11 β-hydroxysteroid dehydrogenase deficiency/inhibition
AME
Licorice and carbenoxolone ingestion
Ectopic ACTH syndrome
?? Essential hypertension variant
?? Pre-eclampsia
Deoxycorticosterone
Congenital adrenal hyperplasia (11-β hydroxylase deficiency and 17-α hydroxylase deficiency)
Glucocorticoid receptor mutations
Metyrapone, mifrestone ingestion

multifunctional, cytochrome P450 enzyme called *aldosterone synthase*, the activity of which normally is suppressed in the zona fasciculata.[6] The absence of aldosterone synthase in the zona fasciculata prevents aldosterone secretion from being regulated by ACTH.

Aldosterone interacts with the mineralocorticoid receptor (MR) to increase sodium transport across epithelial cells of the distal nephron, colon, and salivary gland. The principal cell, located in the cortical collecting tubule, is a key site of potassium regulation and aldosterone activity. The aldosterone-MR complex interacts with the cell nucleus to increase synthesis of aldosterone-induced proteins, and these aldosterone-induced proteins work to open silent luminal Na+ channels and insert new Na+ channels into the lumen.[7-10] Aldosterone also increases the activity and recruitment of basolateral Na+/-K+- adenosine triphosphatase pumps in the principal cell. The resultant increase in Na+ reabsorption promotes K+ secretion via channels in the apical membrane. Aldosterone also stimulates H+ secretion via Na+ transport through its interaction with MRs in the intercalated cells of the kidney cortex.[11]

Of importance, cortisol has a high affinity for the MR. However, target tissues possess enzymes such as 11-β-hydroxysteroid dehydrogenase that converts cortisol to cortisone and other inactive metabolites and, as a result, only aldosterone can activate the MR under normal conditions.[12,13]

Primary Hyperaldosteronism

Primary hyperaldosteronism (PA) is the most common form of mineralocorticoid hypertension and remains a challenging diagnosis for most clinicians. The prevalence has varied from earlier estimates of 0.5% to 2.0% to rates of 10% of hypertensive patients with more widespread screening.[14,15] The prevalence varies by the patient population and the referral center. There are 2 main causes of PA. First, adrenal adenomas present in the adrenal cortex can present with autonomous secretion of aldosterone. The secretion can be in response to either angiotensin II or corticotrophin (ACTH). Bilateral adrenal hyperplasia is the second cause in which aldosterone secretion is exaggerated to the response of angiotensin II.

Screening

Screening is a challenging topic. It generally is advocated that patients with unexplained persistent hypokalemia or with diuretic-induced hypokalemia deserve investigation. An important point, however, is that not all patients with PA present with hypokalemia and some reports claim that only 30% of patients with PA present with hypokalemia.[15] Additional clues may prompt screening in these patients. For example, patients with difficult-to-control hypertension requiring 3 or more medications should be screened. Certainly, patients identified with an incidental adrenal mass should be evaluated. Mosso L, et al[16] advocated screening of all patients with stage 2 and 3 essential hypertension, arguing that the prevalence of PA increases with the severity of hypertension. The prevalence of PA in patients with stage 2 and 3 has been reported to be as high as 8% and 13%, respectively.[16] This screening strategy has been challenged secondary to the increased cost of testing and the increased possibility of false-positive results. This reality must be balanced, however, with identifying patients with a potentially curable form of hypertension or at least, in most patients, partial amelioration of hypertension.

Despite a number of different mechanisms of screening including salt suppression and fludrocortisone-suppression tests, these tests are technically difficult to execute in the outpatient setting. This difficulty often deters clinicians from embarking on a search for PA in patients with low to intermediate risk factors. As a result, the aldosterone renin ratio (ARR) has become the most widespread method of screening.

Japanese investigators first proposed the use of these measurements as a screening test for primary aldosteronism in 1981.[17] Subsequent to the initial report on the use of an ARR as a screening test for primary aldosteronism, other investigators have followed up with additional reports.[18-31] However, data on the sensitivity and specificity of the ARR as a screening test for primary aldosteronism have been complicated by disagreement between investigators on the conditions for screening, how to perform the test, which medications influence the results, and the definition of an ARR cut-off value.

A pooled analysis of available data is contained in the article by Montori and Young,[32] which showed the difficulty in assessing the use of ARR. These investigators conducted a systematic review of the literature (from 1966 to 2001) to establish useful test characteristics (sensitivity, specificity, and likelihood ratios at different cut-off values). Only prospective studies were included in the analysis and a total of 16 studies totaling 3,136 participants were evaluated. The investigators discovered that none of the studies evaluated both the ARR and a reference standard independently (ie, a blinded comparison). In addition, only 2 studies evaluated