Primary Aldosteronism: The Most Frequent Form of Secondary Hypertension?

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In their article in the current issue of *IMAJ*, Benchetrit et al. [1] present 20 normokalemic patients diagnosed with primary aldosteronism. In these patients the basal plasma aldesterone concentration/plasma renin activity ratio of more than 50 suggested hyperaldosteronism. These patients were referred for suppression and stimulation tests (2 L of normal intravenous saline for 4 hours and IV 20 mg furosemide associated with 1 hour standing). Computed tomography revealed normal adrenal glands in 15 patients, however all patients were normalized by spironolactone despite the fact that before this evaluation the patients were defined as having resistant hypertension.

Hypertension, hypokalemia, suppressed PRA and increased aldosterone secretion defined the syndrome of primary aldosteronism when it was first decribed in 1955 [2]. At that time the prevalence of aldosteronism was estimated to be 0.05–2% of the hypertensive population. Thus, only hypokalemic patients were evaluated for the possibility of primary aldosteronism, and a normal PAC ruled out the possibility of primary aldosteronism.

Today, with the availability of modern screening methods, primary aldosteronism seems to be the most common form of secondary hypertension. In 1994 Gordon et al. [3] reported that 8.5% of 199 normokalemic hypertensive patients had primary aldosteronism. The annual incidence of primary aldosteronism at the Mayo Clinic increased more than tenfold over the last 5 years [4].

The elevated blood pressure that is seen in patients with primary aldosteronism is dependent on the mild volume expansion that is usually effectively treated with dietary sodium restriction in human hypertensives. Although aldosterone typically induces sodium and water retention, this volume expansion is followed within a few days by spontaneous diuresis called "aldosterone escape," which returns excretion to the level of intake and partially lowers the extracellular fluid volume toward the normal. The mechanisms of the "escape phenomenon" are not entirely clear. Two major factors may be important: increased secretion of atrial natriuretic peptide stimulated by hypovolemia and by pressure natriuresis, and enhancement of sodium excretion. Persistent hypervolemia also creates increased systemic vascular resistance, which perpetuates hypertension.

In addition to promoting the development of hypertension, hypervolemia promotes suppression of renin release, leading to a very low PRA that is of utmost diagnostic importance. Low

PRA allows us to distinguish between primary and secondary hyper-reninemic forms of hyperaldosteronism, like those that occur in renal, renovascular and diuretic-induced hypokalemia in hypertensive patients.

Although the blood pressure is significantly elevated in most cases of primary aldosteronism, malignant hypertension is a rare occurrence, probably because of suppression of the renin angiotensin system that protects against vascular injury.

Hypokalemia is usually present at some time in most patients with primary hyperaldosteronism. What is the mechanism of hypokalemia and why does it appear only in some patients? Hypersecretion of aldosterone is present in most, if not all, patients with primary hyperaldosteronism. Since aldosterone directly enhances hypersecretion of potassium in the cortical collecting tubule, this cannot explain the diversity of potassium levels in this group of patients, especially when there is no correlation between plasma aldosterone concentration and hypo- or normokalemia. Another factor that contributes to renal potassium wasting, which may be the major factor responsible for the diversity of potassium levels in patients with primary aldosteronism, is adequate delivery of sodium and water to the distal secretory site in the collecting tubule [5]. When sodium intake is increased, exacerbation of hypokalemia occurs, since aldosterone is not suppressed by the expanding volume and more sodium is reabsorbed with additional potasium excretion [6]. If, on the other hand, distal flow and sodium is reduced, then normal potassium balance will be maintained despite aldosterone excess.

Thus we can now understand why patients with primary aldosteronism may present with normokalemia. Since many patients with hypertension and normokalemia are on a low sodium diet, this may prevent appearance of hypokalemia. It is important to remember that occasional patients with primary aldosteronism will not develop hypokalemia even with sodium load. Additional, yet unknown, mechanisms may play a role in potassium balance in primary aldosteronism. However, all patients with aldosteronism, in whom sodium load was performed, responded with changes in serum potassium levels as expected.

For many physicians, hypokalemia became the *sine qua non* of primary aldosteronism; however, even J.W. Conn, the "father" of Conn's disease, described the entity of normokalemic primary aldosteronism years ago [7].

During recent years, determining the PAC/PRA ratio became the basis of the evaluation of patients suspected of having primary aldosteronism, and as a result more non-hypokalemic patients were diagnosed. It has been reported that only in 6 of 16 patients with proven diagnosis of primary aldosteronism was hypokalemia present [8].

It must be mentioned that in glucocorticoid remediable hyperaldosteronism, and in the Liddle syndrome – a rare hereditary disorder in which normal levels of adrenocorticotropic hormone or other non-mineralocorticoid hormones are responsible for excess release of aldosterone – about 50% of the patients present with normokalemic aldosteronism [9].

It seems that primary aldosteronism is the most prevalent cause of secondary hypertension. When only patients with hypertension and hypokalemia were evaluated for this possibility, its prevalence ranged from 0.05 to 2%, but when 199 patients with hypertension were evaluated for primary aldosteronism the prevalence was 8.5% [10]. We therefore recommend that our approach be adopted; namely, that most hypertensive patients with and without hypokalemia, especially those who do not respond to conventional antihypertensive treatment, be evaluated for the presence of primary aldosteronism, which can be defined today as the most prevalent cause of secondary hypertension. As in the study of Benchetrit et al. [1], determination of the PAC/PRA ratio should serve as a screening method. Suppression and stimulation tests should be used at the next stage. The diagnosis of primary aldosteronism is important, since surgical cure has been proven in cases of adenoma, whereas specific medical treatment with an aldosterone antagonist will balance the blood pressure, and physiologic detrimental effects upon the end organs, with gradual tissue damage induced by aldosterone excess, can be prevented.

We conclude that although hypokalemia is still a classic abnormality in the evaluation of possible hyperaldosteronism, all patients with resistant hypertension and normokalemia should also be evaluated for the possibility of primary hyperaldosteronism.

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