Subclinical Primary Aldosteronism

The prevalence of primary aldosteronism (PA) in patients with hypertension has been widely disputed since the syndrome was first described by Jerome W. Conn in 1956. It was originally believed to be rare, but in 1964 Dr. Conn noted that 2 hallmarks of PA, low plasma renin activity (PRA) and adrenal adenomas, were present in many hypertensive persons. He suggested that the prevalence of PA, rather than less than 1%, might be as high as 20% (1).

Within the next few years, low PRA levels were indeed noted in hypertensive patients (2). Increased mineralocorticoid activity was suspected in these patients because of low salivary sodium–potassium ratios, a marker of mineralocorticoid excess (3), and an exaggerated decrease in blood pressure after treatment with aminoglutethimide, a blocker of adrenal steroid hormone production (4), and with spironolactone, an inhibitor of the mineralocorticoid receptor (5). But urinary aldosterone excretion was normal in these patients, so researchers postulated that the suspected mineralocorticoid excess was caused by an unknown mineralocorticoid or by aldosterone, despite its normal levels.

During the 1970s and 1980s, the conception of PA changed in ways that favored more frequent diagnosis. Many cases were reported with unmistakable features of PA, such as complete cure of hypertension after removal of an adrenal adenoma, but with normal potassium levels and high-normal—but nonsuppressible—levels of aldosterone. When diagnosis no longer required hypokalemia and elevated aldosterone levels, many more cases were discovered (6). The simultaneous measurement of aldosterone and PRA, yielding an aldosterone–renin ratio, proved to be an easy and fairly accurate screening test, although often the diagnosis still needed to be confirmed by showing the nonsuppressibility of aldosterone (6).

Also, features of PA were discovered that increased the impetus for greater recognition of the syndrome. Primary aldosteronism proved to be especially common in hypertensive patients with the highest blood pressure elevations and in patients resistant to antihypertensive medications. Patients with PA had higher risk for cardiovascular events than those with essential hypertension and similar blood pressure (6).

Present estimates suggest that PA is present in 5% to 10% or more of persons with hypertension. But it may even be present before hypertension is apparent. A study of 100 normotensive persons, predominantly women, found biochemical markers of PA, including nonsuppressibility of aldosterone and subsequent development of hypertension, in 11 participants (7). But relatively few hypertensive persons are screened for PA (8), owing perhaps to a lack of recognition of the disorder's prevalence and to the complexity of confirmatory testing.

Brown and colleagues (9) used the large and diverse MESA (Multi-Ethnic Study of Atherosclerosis) cohort to identify 850 participants who were normotensive without medication at baseline and had measurements of PRA and serum aldosterone. During the ensuing 5 to 5.5 years, the 392 persons with "suppressed renin activity" (PRA ≤0.50 μg/L per hour) developed hypertension at a higher rate (85.4 cases per 1000 person-years of follow-up) than those with "indeterminate" PRA (53.3 cases) or "unsuppressed" PRA (54.5 cases). Furthermore, despite a lower mean aldosterone concentration than in the other groups, increasing levels of aldosterone were associated with increasing risk for incident hypertension in the suppressed-renin group (but not in the other groups). The suppressed-PRA group was considered to have renin-independent aldosteronism, and the increased incidence of hypertension is evidence that the group did indeed have subclinical PA.

The existence of subclinical PA not only supports the growing evidence that PA is common, it also has other important implications. If normotensive persons with relatively high aldosterone levels due to unrecognized PA were excluded from the reference population, the upper limit of "normal" aldosterone might be lowered, just as the upper limits of thyroid-stimulating hormone are lowered by excluding persons with autoimmune thyroid disease (positive antithyroid antibodies). More hypertensive patients with PA might then fall into the more easily diagnosed category of low renin and high aldosterone, the classic Conn syndrome category that might not require a salt-loading procedure to confirm the diagnosis.

Brown and colleagues' study has significant limitations. Aldosterone and renin were measured while participants had uncontrolled sodium intake, which can lead to wide variation in renin and aldosterone levels. But this variation would be expected to obscure the relation among renin, aldosterone, and blood pressure that was found (that is, bias toward the null). Perhaps more worrisome is the finding that 46% of participants had PRA of 0.50 μg/L or less per hour and 78% had PRA of 1.0 μg/L or less per hour. Such levels are far lower than those seen in persons with hypertension, let alone those without (10). The cause for this unusual finding is not apparent, although the high sodium intake of about 175 mmol per day and the multiethnic population may be factors.

Also unexplained is the low, rather than high, mean aldosterone level in the suppressed-renin group. Aldosterone levels often do not exceed the normal reference range in PA, but they are usually in the upper-normal range. Many guidelines call for a minimum aldosterone level, along with elevation of the aldosterone–renin ratio, before a screening test is considered abnormal (6). We have shown that aldosterone

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levels are not actually "normal" in low-renin hypertension but are both low and high, or bimodal (10). Causes of non–aldosterone-dependent low-renin hypertension (low renin and low aldosterone), such as excess sodium intake or mineralocorticoid excess due to a steroid other than aldosterone, might have caused or contributed to the increased incidence of hypertension in the low-renin group. The low mean aldosterone level suggests that many participants in the suppressed-renin group had non–aldosterone-dependent low renin. One might even wonder whether this study more convincingly shows subclinical low-renin hypertension than subclinical PA.

Despite these limitations, the authors have identified a group of normotensive persons with low PRA and a positive association between aldosterone level and the risk for incident hypertension. Some of these persons very likely have subclinical PA. This observation adds to the increasing evidence that PA is a frequent cause of hypertension, deserving of far more diagnostic attention than it now receives.

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