Primary Aldosteronism and Cardiovascular Events

It Is Time to Take Guideline Recommendations Seriously

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It is nowadays widely accepted that primary aldosteronism is the most frequent cause of endocrine hypertension. Prevalence rates among patients with hypertension are 6% in the primary care setting and 11% in tertiary care referral centers.[1] The 2016 Endocrine Society Practice Guidelines[2] recommend screening of hypertensive subjects with increased pretest probability, which accounts to roughly 50% of all hypertensives. Nevertheless, these recommendations stand isolated and are not fully reflected by current hypertension guidelines in the United States or Europe. More importantly, current healthcare data suggest that little has changed in terms of screening: according to a 2015 survey, only 1% of hypertensives are screened in Italy and 2% in Germany by general practitioners.[3] It is in this context in the current issue of the journal that Ohno et al[4] publish their data from the recently founded Japan Primary Aldosteronism Study.

Using the large data set of 2582 patients with primary aldosteronism, the authors analyzed clinical and biochemical factors associated with prevalent cardiovascular disease. The patients were treated in 15 university hospitals and 14 city hospitals between 2006 and 2016. The data were entered into a nation-wide registry and analyzed retrospectively after rigid chart review. Primary aldosteronism was diagnosed following strict diagnostic criteria, including confirmatory testing and adrenocorticotropic hormone–stimulated adrenal vein sampling. Successful cannulation of both adrenal veins was mandatory for inclusion, using stringent criteria: a selectivity index >5 (corresponding to the ratio of the cortisol concentration in the adrenal vein to that in the inferior vena cava) defined technical success of the procedure, whereas a lateralization index of >4 (aldosterone-to-cortisol ratio of the dominant adrenal side divided by the nondominant side) indicated unilateral aldosteronism. Data of the patient cohort were compared with 2 hypertensive control cohorts: a smaller cohort from the Kyoto Medical Center comprising 236 patients using sex, age, and systolic blood pressure as matching variables and 1263 similarly matched hypertensive subjects of the population-based Nagahama Study. Because of the large number of patients and the careful matching, the study published by Ohno et al[4] has an unprecedented power. It is its first finding that Japanese patients with primary aldosteronism have adverse cardiovascular risk profiles, such as higher body mass index, more prominent proteinuria, and a higher diabetes mellitus rate. This leads to the second finding: patients with primary aldosteronism have strikingly higher rates of cardiovascular disease. The prevalence of cardiovascular disease was 11% versus 3.4% in the matched hypertensive group. This striking difference results from a 3 to 5× higher stroke rate in primary aldosteronism: 7.2% versus 2.5% in the Kyoto Medical Center controls and 8.4% versus 1.6% in the population-based hypertensive control subjects. Especially the high rates of cerebral hemorrhage (2.7%) and subarachnoid hemorrhage (0.5%) are bothersome consequences of long-term uncontrolled hypertension. The third relevant point made by this study is related to potential risk factors predisposing to cardiovascular disease: in multivariate analysis, a low serum potassium ≤3.5 mEq/L was associated with an 1.8-fold risk of adverse outcome, as was unilateral aldosteronism (odds ratio, 1.9) and a baseline plasma aldosterone level of ≥125 pg/mL (odds ratio, 1.9). These data are consistent: more florid cases of primary aldosteronism, that is, aldosterone-producing adenoma, a strong biochemical phenotype, and accordingly low serum potassium levels lead to more cardiovascular comorbidities. This should make it simple for the clinician: clear-cut cases of primary aldosteronism carry the highest risk to develop cardiovascular comorbidities and should be picked up as early as possible.

Why, then, is primary aldosteronism still underdiagnosed? Barriers to appropriate screening of high-risk populations are manifold. There is no clear lead symptom (despite hypokalemia as a late symptom). In the recently published PATO trial (Primary Aldosteronism in Torino),[5] only 29% of patients were hypokalemic. Second, biochemical screening for primary aldosteronism is cumbersome and requires preanalytical considerations. This includes adaptation of hypertensive medication to minimize its influence on the aldosterone to renin, adjustment of salt consumption, and correction of hypokalemia, if present. Third, subtype determination of primary aldosteronism for identification of aldosterone-producing adenoma requires a tertiary referral center offering adrenal vein sampling. Clearly, this remains a major bottle neck in diagnostic workup because few centers are available, and even in so-called expert centers, technical success rate may be discouragingly low.[6]

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(*Hypertension*. 2018;71:413-414.
DOI: 10.1161/HYPERTENSIONAHA.117.10405.)

Hypertension is available at http://hyper.ahajournals.org
DOI: 10.1161/HYPERTENSIONAHA.117.10405

Recent data suggest that unilateral adrenalectomy in patients aged ≤50 years, who have aldosterone-producing adenoma, is associated with excellent hypertension cure rates.[7] Also, it is undisputed that case finding and treatment of primary aldosteronism is cost effective.[8] Moreover, personalized treatment of primary aldosteronism by adrenalectomy or mineralocorticoid receptor antagonist reduces left ventricular mass hypertrophy and microalbuminuria to levels of optimally treated control hypertensives during a time span of >10 years.

In summary, the conclusions taken from the study published by Ohno et al[4] are simple: patients with primary aldosteronism are at high risk for cardiovascular and cerebrovascular events. Patients should be identified early by focusing on high-risk populations as defined by current guidelines,[2] vigorously diagnosed, and treated. This strategy will reduce the burden of disease and save lives.

Sources of Funding

This work was supported by the European Research Council under the European Union Horizon 2020 Research and Innovation Programme (grant agreement No. 694913 to M. Reincke) and by the Deutsche Forschungsgemeinschaft (grant RE 752/20–1 to M. Reincke) and the Else Kröner-Fresenius Stiftung in support of the German Conns Registry-Else-Kröner Hyperaldosteronism Registry (2013_A182 and 2015_A171 to M. Reincke).

Disclosures

None.

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Hypertension
Journal of the American Heart Association

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Hypertension. 2018;71:413-414; originally published online January 22, 2018;
doi: 10.1161/HYPERTENSIONAHA.117.10405
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563