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Update in Endocrinology – Primary Hyperaldosteronism – From Secondary Hypertension Towards Metabolic Syndrome and Beyond

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Primary hyperaldosteronism (PA) was initially considered a rare disease, affecting 1% of hypertensive patients.

Studies published in the last years revealed that PA is the most frequent cause of secondary hypertension, whose prevalence is about 5-12% of the hypertensive population. A higher prevalence (15-20%) occurred in selected patients (type 2 diabetes, resistant hypertension, sleep apnea syndrome) (1). In 100 Asian type 2 diabetic patients with uncontrolled hypertension, prevalence of PA was 13% (2). Prevalence of PA increased from 1.99% in hypertensive patients with SBP 140-159 mm Hg, DBP 90-99 mm Hg to 13.2% in patients with SBP > 180 mm Hg, DBP > 110 mm Hg. A higher prevalence, up to 33.9% was reported in hypertensive patients with sleep apnea syndrome (3).

The large variability in PA's prevalence is due to difficulties in safely withdrawing antihypertensive medications (drugs with minimal effect on renin-angiotensin-aldosterone axis, used to control hypertension during case finding and confirmatory testing for PA are Verapamil slow-release, Hydralazine, Prazosin, Doxazosin, Terazosin) (4). Also differences in aldosterone to renin ratio (ARR) cutoff values, insufficient use of confirmatory tests and bias in the selection of patients could encountered for differences in reported prevalence of PA in various studies (1).

Only a minority of patients (less than one half) presented with hypokaliemia, the majority of patients showing normokalemic hypertension, especially in idiopathic hyperaldosteronism (4).

Epidemiology of PA reflects its pathophysiology: the renin-angiotensin-aldosterone system is involved in linking obesity, dyslipidemia, insulin resistance, chronic kidney disease and hypertension. Hyperinsulinemia and a lipid soluble factor produced by fat tissue stimulate aldosterone' synthesis, and an excess of mineralocorticoids can cause the resistant hypertension observed in diabetic patients (1). On the other hand, aldosterone increases oxidative stress and inflammation, contributing to impaired pancreatic beta-cell function and diminished skeletal muscle insulin metabolic signaling

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(5). Aldosterone excess also displays pro fibrotic effects on small cardiac vessels; it induces endothelial dysfunction, glomerular hyperfiltration, and excess glomerular and tubular leakage of albumin, processes that lead to maladaptive cardiovascular and renal remodeling (1,5).

This explains the increased prevalence of cardiovascular and cerebrovascular complications in PA (34% vs. 11% in essential hypertension): high incidence of myocardial infarction and atrial fibrillation, increased left ventricular mass index with decreased diastolic function, high incidence of stroke (12.9% vs. 3.4%) (1). In 533 patients with PA from German Conn's Registry, 56.1% showed hypokalemia; aldosterone levels, systolic and diastolic blood pressure were significantly higher in hypokalemic patients; prevalence rates for angina (9% vs. 2.1%) or cardiac insufficiency (5.5% vs. 2.1%), were higher in the hypokalemic group (6). In a large series of 3153 patients with ischemic heart disease who underwent coronary angiography (LURIC study), 3.1% of patients had ARR >50. Plasma aldosterone levels stratified in quartiles were significantly associated with all-cause and cardiovascular mortality. Hazard ratio (HR) of all-cause death was higher for quartiles with higher ARR; patients of the fourth quartile had an increased risk of fatal stroke (HR = 7.02). The association of higher plasma aldosterone concentration with overall cardiovascular mortality and sudden cardiac death is stronger for patients with lower kidney function (7).

Mineralocorticoid receptor blockade (Spironolactone, Eplerenone) improves pancreatic insulin release, insulin-mediated glucose utilization, endothelium-dependent vasorelaxation and reduces progression of cardiovascular disease and chronic kidney disease (5).

Recently, progresses were made in the genetic basis of primary hyperaldosteronism. Although PA is largely sporadic, both germline and somatic mutations were described. Somatic mutations affecting the selectivity filter of potassium channel subunit KCNJ5 were found in 41% of 73 cases of aldosteronomas; whose carrying the mutation were larger (1.61 cm vs. 1.04 cm), and consistently lacked a postural aldosterone response, suggesting a physiologically distinct subtype (8). Three germline mutations causing familial hyperaldosteronism have been described, in type I (due to a CYP11B1/CYP11B2 chimera), type II (localized to chromosome 7p22), and type III (mutation in the KCNJ5) familial hyperaldosteronism (9).

In summary, screening for PA should be extended in patients with 2 diabetes mellitus, metabolic syndrome with refractory high blood pressure or sleep apnea syndrome. Screening for PA should not be limited only in hypokalemic, but also in normokalemic hypertensives because high-excess morbidity occurs in both subgroups. The identification of PA is important because these patients have increased cardiovascular and cerebrovascular risks, which can be reduced by proper medical or surgical treatment.

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