Cardiovascular, cerebrovascular and metabolic risk in primary aldosteronism – beyond hypertension

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Received: September 19, 2019, Accepted: November 6, 2019

Abstract
Primary aldosteronism is the most common cause of endocrine hypertension. 5 to 10% of hypertensive patients had primary aldosteronism. Excessive aldosterone production is associated with hypertension, sodium retention, increased potassium excretion that may lead in 9-37% of cases to hypokalemia. Patients with primary aldosteronism have higher cerebrovascular and cardiovascular morbidity and mortality, higher metabolic risk, higher prevalence of sleep apnea, chronic kidney disease, diabetes mellitus, osteoporotic fractures than matched patients with essential hypertension and similar blood pressure values. From the cardiovascular point of view, both normokalemic and hypokalemic primary aldosteronism patients had higher prevalence of left ventricular hypertrophy, angina pectoris, non fatal myocardial infarction, heart failure and atrial fibrillation. In patients with aldosterone producing adenoma (APA), surgical removal of the tumor was associated with improvement of cardiovascular outcome, with similar events to essential hypertension during follow-up. By contrary, patients with bilateral idiopathic primary aldosteronism treated with mineralocorticoid receptor antagonists (spironolactone, eplerenone) showed persistent increased cardiovascular risk during follow-up if plasma renin activity remained suppressed (<1 μg/L/h). In patients treated with higher mineralocorticoid receptor doses, leading to unsuppressed plasma renin activity (≥1 μg/L/h), cardiovascular outcomes were similar to essential hypertension patients. Due to increased prevalence, high cardiovascular, cerebrovascular and metabolic complications associated to primary aldosteronism, efforts should be made for a proper screening (especially in patients with resistant hypertension, sleep apnea), an early diagnosis, a proper lateralization and treatment, in order to improve the outcome of these patients.

Keywords: primary aldosteronism, secondary endocrine hypertension, renin, non fatal myocardial infarction, heart failure, atrial fibrillation.

Introduction
Primary aldosteronism (PA) is the most frequent cause of endocrine secondary hypertension [1]. It is characterized by autonomous aldosterone secretion, that is independent of renin, angiotensin II and sodium and potassium status. Excessive activation of the mineralocorticoid receptor lead to volume expansion, hypertension and in advanced stages to hypokalemia and metabolic alkalosis [2]. It affects about 10% of hypertensive patients (4-19%) and about 20% of patients with resistant hypertension [3].

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Primary aldosteronism is associated with increased risk of cardiovascular and cerebrovascular events, with increased metabolic risk (including diabetes mellitus and metabolic syndrome), with increased risk for chronic kidney disease and sleep apnea, with increased risk for osteoporotic fractures. Target organ damage (heart, kidney, brain) is higher than in patients with essential hypertension [1]. This is due to inflammation, oxidative stress, insulin resistance, endothelial dysfunction and fibrosis associated with primary aldosteronism [4].

In PA cases submitted to selective adrenal venous sampling, lateralization of aldosterone hypersecretion permits the diagnosis of aldosterone producing adenoma (APA). When there is no clear lateralization, the patients were considered having bilateral adrenal hyperplasia BAH). APA patients were submitted to surgical adrenalectomy, while patients with BAH received medical treatment with mineralocorticoid receptor antagonists (spironolactone or eplerenone) [5].

Complications in primary aldosteronism are more frequent than in essential hypertension with the same severity of increased blood pressure. Target organ damage, cardiovascular, cerebrovascular and renal complications more prevalent than in essential hypertension with same blood pressure values are a solid argument for screening for primary aldosteronism in risk population [5,6]. Both normokalemic and hypokalemic primary aldosteronism are associated with increased risk of comorbidities [7].

Cerebrovascular events

In a series of 533 patients with primary aldosteronism from the Conn syndrome registry, prevalence of cerebrovascular events was 12.6% in hypokalemic PA patients and 13.2% in normokalemic PA patients. Prevalence of stroke was higher in normokalemic PA patients than in hyokalemic ones (7.8% vs. 4.2%) [7].

A meta-analysis of 31 studies, 3838 patients with PA vs. 9248 patients with essential hypertension, followed-up for 8.8 years after hypertension diagnosis confirmed the results of previous study: PA patients showed an increased risk for stroke (OR= 2.58, 95% CI= 1.93-3.45) [8].

Cardiovascular events

Prevalence of all cardiac events is higher in patients with hypokalemic PA (35.2% vs. 20.2%). Both angina pectoris and chronic cardiac insufficiency were more prevalent in hypokalemic than in normokalemic PA patients (9% vs. 2% and 5.5% vs. 2.1%, respectively). PA patients also showed increased prevalence of myocardial infarction (3.6-4.1%), atrial arrhythmias (7.8-12.3%). Interestingly, prevalence of ventricular arrhythmias was similar in hypokalemic and normokalemic PA (1.9% vs. 2.1%) [7].

Comparing 459 patients with primary aldosteronism and 1290 control patients with essential hypertension matched for gender, age (± 2 years) and office systolic blood pressure (± 10 mm Hg) in a controlled cross-sectional study, Savard and co-authors found in PA increased risk of electrocardiographic and echocardiographic left ventricular hypertrophy (odds ratio= 2 after adjustment for hypertension duration), coronary artery disease (adjusted OR= 1.9), non fatal myocardial infarction (adjusted OR= 2.6), heart failure (adjusted OR= 2.9) and atrial fibrillation (adjusted OR=5). The increased cardiovascular risk was similar across plasma potassium levels and plasma aldosterone concentration [6].

A recently published meta-analysis of 31 studies (3838 patients with PA vs. 9248 patients with essential hypertension) confirmed the results of previous studies: PA patients showed an increased risk for stroke (OR= 2.58, 95% CI= 1.93-3.45, coronary artery disease (OR= 1.9), non fatal myocardial infarction (OR= 2.6), heart failure (OR= 2.9) and atrial fibrillation (OR=5). The increased cardiovascular risk was similar across plasma potassium levels and plasma aldosterone concentration [6].

Mechanisms by with aldosterone excess favors onset of atrial fibrillations and heart failure are multiple: effects on cardiomyocytes (representing up to 75% of myocardial tissue) with left ventricular hypertrophy and left ventricle diastolic dysfunction; effect of macrophages, promoting inflammation, necrosis and reparative fibrosis; effects on myofibroblasts and vessel endothelial cells enhancing extracellular matrix, promoting fibrosis, electrical heterogeneity and re-entry circuits; in hypokalemic PA patients, there is also and increased PQ interval, and increases A wave and decreased E wave duration leading to changes in left ventricle filling pattern [9].

Treatment influence on cardiometabolic outcomes

When comparing cardiovascular and cerebrovascular events (myocardial infarction, coronary...
artery disease, stroke, transient ischaemic attack, arrhythmias, heart failure) in 270 patients with PA (57 aldosterone producing adenomas - APA and 213 bilateral adrenal hyperplasia- BAH), with a control group (n= 810 patients with essential hypertension), total events were more frequent in PA group (22.6% vs. 12.7%, p < 0.001). The events were more frequent in PA both at diagnosis (14.1% vs. 8.4%) and during follow-up (8.5% vs. 4.3%). Patients with APA treated by surgery showed increased prevalence of total events and increased prevalence of events at diagnosis, but after surgical removal of APA, the number of events was similar to essential hypertension. By contrary, patients with BAH medically treated with mineralocorticoid receptor (MR) antagonists showed higher prevalence of total events and higher prevalence of events during follow-up [10].

In a series of 602 patients with PA treated by mineralocorticoid antagonists (no lateralization or unsatisfactory or indeterminate lateralization in 84% of patients in whom adrenal vein sampling was performed) compared with 41853 age-matched patients with essential hypertension, the authors reported an increased prevalence of composite cardiovascular events (56.3 vs. 26.6 events/1000 person-years): myocardial infarction or coronary revascularization (multivariate adjusted hazard ratio = 1.81), hospital admission for congestive heart failure (HR= 1.61) and cerebrovascular accident or transient ischaemic attack or transient ischaemic attack (HR= 2.38). Also the incidence of atrial fibrillation (HR= 1.93), diabetes mellitus (HR= 1.26) and total mortality (HR= 1.34) were increased in medically treated PA patients as compared with essential hypertension ones. The excess risk for composite cardiovascular outcomes and mortality was limited to PA patients whose plasma renin activity remained suppressed (<1 μg/L/h) on medical treatment with mineralocorticoid receptor antagonists (adjusted HR= 2.83, 95% CI= 2.11-3.8 and adjusted HR= 1.79, 95% CI= 1.14-2.8, respectively), while PA patients treated with higher mineralocorticoid receptor antagonists doses, who had unsuppressed plasma renin activity (≥1 μg/L/h), had similar outcomes with essential hypertension patients [11].

Similar data were reported for atrial fibrillation: HR for atrial fibrillation is 2.55 for patients with medically treated PA patients whose plasma renin activity (PRA) was < 1 μg/L/h compared with essential hypertension and HR= 1.03 for PA patients whose PRA was ≥1 μg/L/h. Moreover, PA patients treated by sugery showed even lower incidence of atrial fibrillation (HR= 0.75) as compared with essential hypertension patients [12].

In the PAPY study population, atrial fibrillation free survival was significantly higher in patients with essential hypertension than in patients with PA and in patients with PA due to idiopathic hyperaldosteronism who were medically treated. However, atrial fibrillation free survival was similar in patients adrenalectomized for APA and in patients with essential hypertension. This was the first study to show that adrenalectomy lowered incident atrial fibrillation in primary aldosteronism patients [13].

**Diabetes mellitus and metabolic syndrome**

In PA there is an increased prevalence of glycaemic disorders as compared with essential hypertension (OR= 1.55). Meta-analysis of 16 studies found an increased prevalence of impaired fasting glucose (31.2%), impaired glucose tolerance (26.19%) and diabetes mellitus (15.2%). PA patients showed a lower level of insulin sensitivity in comparison with the normal group and an increased insulin resistance (presented by HOMA index) compared with normal controls, but weaker than in essential hypertension group [14].

Increased prevalence of both diabetes mellitus and impaired glucose tolerance was also reported in a series of 117 PA patients compared with 117 patients with essential hypertension (41.9% vs. 17.1%). Prevalence of metabolic syndrome was also higher in PA (51.3% vs. 24.8%). Basal insulin secretion index (HOMA β) was decreased in PA compared with essential hypertension, but only mass index, triglycerides, LDL cholesterol were significantly increased in essential hypertension compared with PA [15].

In a recently published paper, prevalence of type 2 diabetes mellitus in PA patients was significantly higher than that in EH patients (22.8% vs. 12.2%, P<0.05), especially in middle-aged and old patients and in patients with hypokalemia. However, prevalence of metabolic syndrome was similar [16].

In a series of Romanian patients with PA, we found a positive correlation between fasting glycaemia and plasma aldosterone and a negative
correlation between fasting glycaemia and serum potassium levels [17].

In a series of 152 PA patients, Hanslik and co-authors found a negative correlation between serum potassium concentration and the 2 h oral glucose tolerance test glucose concentration [18].

Pathogeny of hyperglycemia in primary aldosteronism implied a direct negative effect of aldosterone excess on β cells function, direct negative effect of aldosterone excess on insulin receptor in adipose tissue and hepatocytes (insulin resistance), direct effect of aldosterone through collagen deposition and fibrosis in pancreas, liver, adipose tissue and muscles. Hypokalemia also lead to altered tissue insulin response at insulin and altered insulin secretion. After adrenalectomy, improvement of first phase of insulin secretion induced by glucose was reported. Both surgery and spironolactone treatment improved altered response to insulin [23].

Chronic kidney disease
There is an increased prevalence of chonic kidney disease both in patient with normo and hypocalemic PA (6.6-6.8%) [7].

Patients with PA showed significantly higher 24-hour urinary albumin excretion (UAE) than in hypertensive controls and relative glomerular hyperfiltration. Glomerular hyperfiltration was considered to underestimate renal damage in PA. In 213 PA patients (102 APA and 111 cases with bilateral hyperaldosteronism, prevalence of chronic renal disease was 15.7% in APA and 8.1% in bilateral hyperaldosteronism at the first visit and significantly increase to 37.1% and 28.3% one year after treatment. Higher UAE and lower serum potassium levels were independent predictors of decreasing estimated glomerular filtration rare one year after treatment [24].

In a larger series of 505 PA patients, 202 submitted to adrenalectomy and 303 patients on MR antagonists from the Japan Primary Aldosteronism Study, the increased age, low serum potassium levels, high eGFR, and high plasma aldosterone levels were independent predictors for a large initial eGFR fall in both group. However, in patients on MR antagonists, cases with a small initial eGFR fall had a significantly steeper long-term eGFR slope than those with a large initial fall (tertile 1 versus 2, P=0.025; tertile 1 versus 3, P=0.017) [25].

Autoimmune diseases
There is an increased incidence of new onset autoimmune diseases in PA compared with matched EH (HR= 3.82), in APA compared with matched EH (HR= 2.96). The risk of incident new onset
autoimmune diseases remained increased in patients treated by adrenalectomy (HR=3.1) or MRA (HR=4.04) compared with matched essential hypertension controls and followed-up for a mean of 8.9 years[26].

Conclusions

For similar blood pressure elevation, primary aldosteronism was associated with a worse cardiovascular, cerebrovascular, metabolic and renal outcome, as compared with essential hypertension. Adrenalectomy improved vascular outcome, so efforts should be made for an early diagnosis, for a correct lateralization and referral to adrenalectomy. In patients treated with mineralocorticoid receptor antagonists, the therapy goals should be serum potassium normalization, normalization of blood pressure and obtaining a plasma renin activity higher than 1 ng/ml/hour.

Abbreviations

PA= primary aldosteronism
APA= aldosterone producing adenoma
EH= essential hypertension
MRA= mineralocorticoid receptor antagonist
OR= odds ratio
HR= hazard ratio
UAE= urinary albumin excretion

Conflict of interest

The authors confirm that there are no conflicts of interest.

References


