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Primary hiperaldosteronism – incidence and impact on heart and kidney

Pierwotny hiperaldosteronizm – częstość występowania oraz wpływ na serce i nerki

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S u m m a r y

For over five decades after first description of Litynski and clinical characterization by Conn, primary hyperaldosteronism (PA) was generally regarded as a relatively rare cause of hypertension (HT), present in less than 1% of all patients.

Available evidence clearly indicate that the prevalence rate of primary hyperaldosteronism vary from 4.6 to 16.5% in those studies in which confirmatory tests to diagnose were used.

Enormous progress has been made over the past decades in understanding pathogenesis and genetic background, clinical course and cardiovascular complications of this most common cause of secondary HT.

There is also growing body of experimental and clinical studies indicating that prolonged exposure to elevated aldosterone concentration is associated with target organ damage particularly in the heart and kidney. Current evidence convincingly demonstrates that both surgical and medical treatment strategies beneficially affect target organ damage and cardiovascular outcomes and mortality in the long term observation.

S t r e s z c z e n i e

Na przestrzeni pięciu dekad od czasu pierwszych opisów choroby dokonanych przez Lityńskiego oraz Conna, pierwotny hiperaldosteronizm uznawany był za relatywnie rzadką przyczynę wtórnego nadciśnienia tętniczego, występującą u mniej niż 1% chorych.

Zgodnie z obecnym stanem wiedzy częstość występowania pierwotnego hiperaldosteronizmu w badaniach z wykorzystaniem testów potwierdzających rozpoznanie waha się między 4,6 a 16,5%.

Na przestrzeni ostatnich dekad dokonał się znaczący postęp w zrozumieniu patogenetycznego i genetycznego podłoża, przebiegu klinicznego oraz powikłań sercowo-naczyniowych tej najczęściej występującej przyczyny wtórnego nadciśnienia tętniczego.

Wyniki znaczącej liczby dotychczas przeprowadzonych badań eksperymentalnych i klinicznych wskazują, że podwyższone stężenie aldosteronu ma związek z rozwojem powikłań narządowych, szczególnie w obrębie serca i nerek. Dotychczas zgormadzone dane potwierdzają, że wdrożenie zarówno chirurgicznego, jak i farmakologicznego leczenia pierwotnego hiperaldosteronizmu może korzystnie wpływać na powikłania narządowe, występowanie zdarzeń sercowo-naczyniowych oraz śmiertelność w obserwacji odległej w tej grupie chorych.

Conflict of interest
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INTRODUCTION

For over five decades after first description of Litynski and clinical characterization by Conn, primary hyperaldosteronism (PA) was generally regarded as a relatively rare cause of hypertension (HT), present in less than 1% of all patients. However over the past 20 years the prevalence of this clinical condition has been reported to be much higher and is ranging from 10 to 30% in highly selected groups (1-3).

Enormous progress has been made over the past decades in understanding pathogenesis and genetic background, clinical course and cardiovascular complications of this most common cause of secondary HT (3, 4).

Of special note to our current knowledge in PA is the contribution of one of the most distinguished polish clinician and scientist Franciszek Kokot whose classic studies in this field are widely recognized in the world literature. It should be noted that in early 70ties of XX century Kokot et al. presented in Poland the first detailed clinical description of a large group of patients with PA (5, 6).

A substantial body of experimental and clinical evidence about long-term effects of aldosterone excess on the cardiovascular and renal system has been gathered over the last years (3).

Increasing aldosterone levels promote renal sodium retention, potentiate the actions of angiotensin II, impair

endothelial function and reduce vascular compliance. Several experimental investigations in salt fed animals documented profibrotic and pro-hypertrophic effects of aldosterone independent of arterial blood pressure (BP) level and circulating plasma volume (1, 2).

Landmark experiments demonstrated that chronic aldosterone infusion causes myocardial fibrosis in rats that are maintained on high-salt diet. In regard of left ventricule hypertrophy (LVH) as an independent risk factor, studies in patients with PA revealed relationship between circulating aldosterone levels and cardiac structure (7-9).

It has been also documented in uninephrectomized and stroke-prone spontaneously hypertensive rats that aldosterone produced intrarenal vascular damage, glomerular injury and tubulointerstitial fibrosis. The animal studies consistently indicate that aldosterone causes tissue damage in the context of inappropriate salt status and might depend on mineralocorticoid receptor (MR) activation reflecting in different tissues increased oxidative stress and impairment of 11 beta-HSD2 activity (10-12).

Therefore, growing body of evidence suggests that exposure to inappropriate aldosterone levels for salt status and/or activation of the MR can produce myocardial and renal tissue injury involving mechanisms that are independent of BP (10).

It has been documented that absolute aldosterone excess in patients with PA has been associated with higher risk of heart, vascular and kidney damage resulting in increased total cardiovascular risk. Also the prevalence of cardiovascular events is higher in patients with PA as compared to those with essential hypertension (EH) (3).

PREVALENCE

Recent epidemiological studies have shown that serum aldosterone and renin levels and the aldosterone/renin ratio (ARR) correlate with increased BP and the incidence of HT in the general population (3, 13).

Examination of large, community-based sample of nonhypertensive persons showed that increasing aldosterone levels within physiologic range may influence BP and may predispose to hypertension. Recent study documented that in a large cross-sectional cohort of patients ARR determined peripheral and central BP values over a broad range (13).

It is generally accepted that the prevalence of PA varies considerably between different studies among patients with hypertension, depending on patients selection, diagnostic methodology used and severity of arterial HT (3, 14).

Numerous cross-sectional and prospective studies in unselected hypertensive populations have documented that the prevalence of PA is much higher than previously believed and varies significantly between studies ranging from 4.6 to 16.6% when confirmatory tests to diagnose PA were employed (13).

A step-wise increase in the prevalence of PA according to the severity of systolic and diastolic BP elevations has been observed. In the study of Mosso et al. the prevalence of PA varied depending on the severity (stage) of hypertensive disease as defined by the JNC VI. The results showed that the prevalence was similar to that found in normotensive subjects or those with stage 1 (1.99%) but was significantly higher in stages 2 (8.55%) and 3 (13.5%) of the disease (15).

Also PAPY study documented that at the screening test the proportion of patients with PA caused by both APA and IHA increased significantly from 7.2 to 19.5% with the increasing severity of hypertension from grade 1 to grade 3 (16).

However it is still a subject of debate, it has been commonly agreed that resistant hypertension is the condition with the highest probability of detection of PA (3).

Douma et al. documented in a large group of patients with resistant hypertension that although the ARR was positive in about 20% of patients with resistant hypertension, after confirmatory tests the diagnosis resulted in the prevalence of 11.3% in the total study population (17).

Also in the RESIST-Pol study increased ARR was present in 28.4% of and the diagnosis of PA was further confirmed in 15.7% subjects (18).

The results from two German epidemiological studies indicate that the frequency of positive screening results in the subgroup of subjects with resistant hypertension was 11.9% being consistent with other studies (3).

Taken together, many methodological factors may be responsible for the wide variation in the prevalence of PA in hypertensive patients, as they depend on patients selection and can interfere with renin and/or aldosterone measurements affecting the diagnostic accuracy of both screening and diagnostic tests (19, 20). Factors such as posture at the time of sampling, serum potassium levels, renin/aldosterone assays employed, renal function, gender, age and use of antihypertensive drugs are all known to be implicated (21).

CARDIOVASCULAR RISK AND IMPACT ON THE HEART AND KIDNEY

A growing body of data coming from longitudinal, retrospective studies supports the presence of increased prevalence of cardiovascular complications in patients with PA as compared with those with EH (7, 8, 10).

In particular, a substantial body of experimental and clinical evidence about the long-term effects of excess aldosterone on the heart and kidney was gathered over the past years (7, 8, 10).

Recently it has been reported that at baseline the prevalence of cardiovascular events was higher in PA than in EH with odds ratios of 4.93, 4.36 and 2.80 for sustained arrhythmias, cerebrovascular events and coronary heart disease respectively. Also, the prevalence of cardiovascular complications was comparable in patients with APA and idiopathic disease clearly documenting that patients with both subtypes are at increased risk (22).

The authors also evaluated long-term cardiovascular outcomes in patients with PA after surgical or medi-

cal treatment and during mean duration of follow-up of 7.4 years cardiovascular outcome was not different between patients with PA and EH and was comparable in PA between patients with APA and IHA (22).

Also recent data from the German Conn's Registry indicate that in patients with PA the prevalence of cardiovascular events – including angina pectoris, myocardial infarction, chronic cardiac insufficiency, coronary angioplasty – was 16.3%. Although the German study lacked a reference matched control group, in patients with PA the prevalence of cardiovascular complications was greater than that reported in the literature for patients with EH of comparable cardiovascular risk profile (23).

The study documented that cardiovascular mortality is increased in patients treated for PA – however after matching for age, sex, BMI or BP the data showed that all-cause mortality in patients with PA was not significantly different from matched hypertensive controls (23).

IMPACT ON THE HEART

Due to the presence of clinical and subclinical organ damage in PA, the aim of the treatment should not be confined to normalization of BP and correction of hypokalemia, but also extend for prevention of cardiovascular and renal complications (7, 10).

Numerous experimental studies documented the presence of mineralocorticoid receptors in cardiomyocytes and their activation might be related to myocardial hypertophy in PA involving mechanisms of accelerated fibrosis and modulation of ionic movements (7-9).

The latter mechanism might in turn result from interactions of aldosterone with other hormones including angiotensin II, endothelin, bradykinin, activation of inflammatory cells and stimulation of fibroblast proliferation and collagen synthesis (7-9).

Interruption of these receptor-mediated mechanisms might explain why in the long term treatment of PA with MR receptor antagonist has comparable effects with the removal of the aldosterone – secreting adenoma in reducing LV mass although this response occurs later than after adrenalectomy (24).

Several studies documented structural and functional changes of the heart in patients with PA and particularly cross-sectional echocardiographic studies have shown increase of left ventricular (LV) mass in patients with PA as compared to other forms of hypertensive disease although this finding has not been confirmed in all studies (25-27).

It has been reported that the incidence of inappropriate LV mass is increased in patients with PA, even in the absence of LV hypertrophy defined by the current criteria. This observation supports the concept that increased aldosterone level contributes to the increase in LV mass (27).

In PA, LV hypertrophy occurs in association with an abnormal pattern of LV filling indicating the presence of diastolic dysfunction whereas systolic function in generally found to be comparable with the patients with essential hypertension. Furthermore the diastolic dysfunction of PA has been associated with the evidence of abnormal videodensitometric properties of LV wall, suggesting myocardial fibrosis (25).

It is generally accepted that all these aldosterone-related cardiac abnormalities could contribute to the augmented cardiovascular risk observed in patients with PA and account for greater incidence of arrhythmia, cerebrovascular disease and heart failure (10).

Mechanisms causing more frequent CAD are only hypothetical including proinflammatory effects of aldosterone on arterial wall, excess LV hypertrophy with increased oxygen consumption, endothelial dysfunction and remodeling of resistance vessels (8).

It is of note that most of echocardiographic observations of cardiac changes after treatment of PA are limited to studies with short-term follow and particularly after removal of adrenal adenoma. Available observations indicated that in patients with APA treated by adrenalectomy, both LV mass and LV filling patterns were normalized 12 months after surgery in contrast to those who were treated for a year with spironolactone and showed no comparable LV hypertrophy regression (28).

A recent study with long-term follow has shown significant decrease of LV mass in 45 patients with PA who have been re-evaluated after an average follow-up of 36 months either surgery or treatment with spironolactone. It is of interest that regression of LV mass in adrenalectomized patients occurred earlier than those treated with spironolactone (29).

Consistent with this findings, the another long-term study with 7 year observation has demonstrated that patients treated either with adrenalectomy or spironolactone have significant and comparable decrease of LV mass, although decrease is significant within the first year only after surgery. In both treatment groups, baseline LV mass was correlated with plasma aldosterone concentration, which was independent predictor of changes of LV mass after the treatment (30).

In summary, there is a growing body of evidence supporting detrimental effect of high aldosterone levels on structural and functional changes of the heart in patients with PA. It has been also demonstrated that the decrease of LV mass obtained with treatment of PA is only partially explained by blood pressure reduction and clearly indicating a role of aldosterone that is independent of the hemodynamic overload (3).

IMPACT ON THE KIDNEY

Experimental studies in animal models have demonstrated that inappropriate aldosterone levels for sodium status can produce extensive renal damage. Furthermore clinical studies indicate that PA is associated with renal complications that reflect the capability of elevated aldosterone to induce kidney dysfunction beyond what could be expected from BP elevation (10).

It should be noted that relationship between kidney and clinical course of PA deserves attention because

structural renal damage may be associated with unfavorable outcomes and possibility to develop progressive renal failure. However early involvement of the kidney in PA is characterized by functional changes which are largely reversible with treatment (10, 11).

Relevant information has been obtained from two prospective studies of Sechi et al. and Ribstein et al. with different follow-up after treatment and have consistently indicated that PA is characterized by partially reversible renal dysfunction (31, 32).

In the study with short-term follow-up Ribstein et al. documented a significant decrease in urinary albumin excretion after adrenalectomy in 25 patients with adrenal adenoma who were followed up for 6 months. The authors concluded that PA was associated with relative hiperfiltration unmasked after suppression of aldosterone excess (32).

The authors also investigated the effect of surgical and medical treatment of PA on GFR and documented that GFR was reversed after the surgical and medical treatment of PA, a finding that has been subsequently confirmed in larger cohorts of patients with PA and recent meta-analysis (32, 33).

In the long-term observation Sechi et al. reported that in 50 patients with PA, GFR and albuminuria were higher at baseline in patients with PA than those with EH. In the follow-up of mean of 6.4 years microalbuminuria was more likely subsiding to normal levels after treatment than progressing to overt proteinuria (31).

Sechi et al. study documented that during the 6 month after intervention the mean GFR decreased by -13.6 ml/min in patients with PA but only -2.1 ml/min in patients with EH but subsequent declines in GFR were similar in this study in patients with PA and EH during next 9 year follow-up (31).

The German Conn's Registry gave evidence for lower GFR in untreated patients with PA compared with age, BMI and sex – matched hypertensives from a population in southern Germany. Regression analysis showed that age, male sex, low potassium and high aldosterone concentrations were independent predictors of lower GFR (33).

The data from the German Conn's Registry confirm this observation and showed that GFR declined soon after treatment of PA and remained relatively stable thereafter. Analysis of renal outcomes in patients with PA who were treated with adrenalectomy or spironolactone did not reveal significant difference (33).

Taken together these data suggest that effective surgical or medical treatment of removes renal hiperfiltration and may uncover the real extent of renal damage associated with PA.

CONCLUSIONS

Available evidence clearly indicate that the prevalence rate of primary hyperaldosteronism vary from 4.6 to 16.5% in those studies in which confirmatory tests to diagnose were used.

There is also growing body of experimental and clinical studies indicating that prolonged exposure to elevated aldosterone concentration is associated with target organ damage particularly in the heart and kidney. Current evidence convincingly demonstrates that both surgical and medical treatment strategies beneficially affect target organ damage and cardiovascular outcomes and mortality in the long term observation.

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