REVIEW ARTICLE

Primary aldosteronism: a new insight into pathogenesis, diagnosis, and treatment in hypertensive patients

Lidia Hyla-Klekot[1], Franciszek Kokot[2]

1 Pediatric and Oncological Center, Chorzów, Poland
2 Department of Nephrology, Endocrinology and Metabolic Disease, Silesian Medical University, Katowice, Poland

KEY WORDS

diagnosis, prevalence, primary aldosteronism, therapy

ABSTRACT

Primary aldosteronism (PA) seems to be a pathogenetically heterogenous disease. It is suggested that approximately 30% of all hypertensive patients are affected by this disease. Autonomous hypersecretion of aldosterone, which is observed in this patient group, may be caused by an adrenal adenoma (aldosteronoma), hyperplasia of the zona glomerulosa, mutation of the KCNJ5 potassium channel, or other rare pathogenetic factors. Contrary to what was believed before, PA may be the cause of resistant hypertension rather than mild hypertension, while 70% of the patients have normal serum potassium levels rather than hypokalemia (previously believed to be a classical PA symptom). Hypertensive patients with normal or elevated aldosteronemia (A), suppressed plasma renin activity (PRA) and an elevated A/PRA ratio should undergo further diagnostic work-up for PA. PA is suspected to be the continuum of low-renin hypertension. First-choice therapy of PA should be based on long-term administration of low-dose mineralocorticoid receptor antagonists (spironolactone, eplerenone) and, in the nearest future, probably also aldosterone synthase antagonists such as CLI699, regardless of the morphological type of PA. It is still unknown whether pharmacological treatment will totally replace surgical treatment in some types of PA. Long-term administration of low-dose aldosterone antagonists is an effective and often underscored antihypertensive treatment, which rarely causes serious hyperkalemia if the kidney function is not impaired.

Introduction Arterial hypertension is a disease symptom that develops in 15% to 30% of the Caucasian population and its incidence increases with age. Therefore, it is not surprising that cardiovascular, renal, and cerebral complications are nowadays the leading cause of death in adult population. Despite intensive research and discovery of important pathogenetic factors, the treatment of arterial hypertension remains rather symptomatic. Hypervolemia and increased resistance of blood vessels as well as known hypertension-related factors associated with these links are the most common targets of pharmacotherapy. Among hypertension-related factors, salt consumption as well as increased activity of the individual components of the renin–angiotensin–aldosterone (RAA) system and of the sympathetic system play a significant pathogenetic role.

Of these factors, aldosterone is particularly important for at least 3 reasons: 1) the role of this hormone under physiological and pathological conditions has been relatively well elucidated; 2) it is the major factor responsible for arterial hypertension in such pathological conditions as primary aldosteronism caused by adenomas (aldosteronomas) or cancers, and, more rarely, aldosteronism treatable with glucocorticosteroids (glucocorticosteroid remediable aldosteronism); and 3) pharmaceutical agents that effectively block the synthesis of aldosterone (the hormone itself or its receptor) have been discovered.

Primary hyperaldosteronism is a type of secondary hypertension, in which the elimination of the hypertension-related factor (elimination of the cause of autonomic aldosterone hypersecretion) is associated with a high likelihood of

Correspondence to:
Prof. Franciszek Kokot, MD, PhD, Katedra i Klinika Nefrologii, Endokrynologii i Chorób Przemiany Materii, ul. Francuska 20, 40-027 Katowice, Poland, phone/fax: +48-32-259-14-20, e-mail: fkokot@spskm.katowice.pl
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the permanent normalization of blood pressure in a large proportion of the patients (about 50%).

This paper aims to present the following aspects of primary aldosteronism (PA) in a concise way: 1) physiology and pathology of aldosterone; 2) diagnosis of PA (differential diagnosis with low-renin essential hypertension); 3) prevalence of PA; and 4) treatment of PA.

We only discuss several papers, mostly reviews published in the last couple of years. We refer all readers interested in this topic to our other reviews[1,2] that present the state of knowledge on this issue until 2008.

Physiology and pathology of aldosterone Aldosterone is mainly produced by the zona glomerulosa cells in the adrenal glands. Factors stimulating the secretion of this hormone include angiotensin II, hyperkalemia, and adrenocorticotropic hormone. The kidneys were thought to be the main target organ for aldosterone because it stimulates reabsorption of sodium and secretion of potassium by distal nephron cells. By binding with cytoplasmic receptors, aldosterone is the main regulator of transcription of numerous genes. Apart from a classical genomic pathway, many other signaling pathways mediated by aldosterone, insensitive to transcription or translation inhibitors and rapidly initiated, have been discovered. Those signaling pathways are described as non-genomic. They are linked with the mineralocorticoid receptor (MR) or with a specific membrane receptor. There is a constant "cross-talk" between genomic and non-genomic signaling pathways.[1-3]

MR is present not only in the kidneys but also in many extrarenal cells such as cardiomyocytes, endothelial cells, vascular myocytes, adipocytes, and macrophages. Apart from the adrenal glands, aldosterone synthesis has been demonstrated in numerous organs, including the heart, and in the perivascular adipose tissue.[1-3]

Apart from classical renal effects (i.e., those on water-electrolyte and acid-base metabolism), aldosterone shows nephrotoxic (it stimulates progression of different nephropathies) and proinflammatory activity; moreover, it has fibrotic effects in the heart and vessels. Factors increasing these effects include, among others, increased supply of sodium, angiotensin II, and oxidative stress. Moreover, the presence of the inflammatory processes and macrophage infiltration is indispensable for the development of heart fibrosis. In addition, it has been demonstrated that aldosterone and activation of MRs are equally responsible for metabolic syndrome, insulin resistance, and vascular remodeling favoring atherosclerosis progression. Furthermore, via a non-genomic pathway, aldosterone is involved in impaired synthesis of nitric oxide by the endothelial cells, increased stiffness of the vessels, adipocyte proliferation, activation of the RAA system, and increased synthesis of proinflammatory cytokines and metabolites of oxidative stress in the adipose tissue.[1-3]

Diagnostic criteria of primary aldosteronism PA results from autonomic hypersecretion of aldosterone by the zona glomerulosa cells in the adrenal glands. Morphological changes of the adrenal glands observed in patients with PA include single or multiple adenomas (APA) consisting of the zona glomerulosa cells, micro- or macronodular hypertrophy of the zona glomerulosa, or general hypertrophy of the zona glomerulosa cells of one or both adrenal glands. These cells are the site of increased aldosterone secretion. In the majority of patients with zona glomerulosa hypertrophy, adrenal medullary hypertrophy is also observed. This finding may suggest a role of catecholamines in the pathogenesis of zona glomerulosa hypertrophy.[4]

Although the Polish literature presents a description by Lityński[5] of 2 cases of patients with arterial hypertension in whom macronodular hypertrophy of the zona glomerulosa of 1 adrenal gland (in 1 deceased patient) or both adrenal glands (in the other deceased patient) was found, it is Conn[6] who is considered to have discovered PA because he proved that arterial hypertension in these patients was caused by aldosterone, a substance that was not assessed by Lityński in 1953.

In accordance with the description by Conn in 1955[6] and reports by other authors in the subsequent years, PA was assumed to be a rare cause of moderate or mild arterial hypertension, responsive to pharmacological treatment. Hypokalemia and increased aldosteronuria (blood aldosterone levels were not yet estimated in the 1950s) as well as low plasma renin activity (PRA) were considered to be the leading diagnostic features of this clinical syndrome. It soon turned out that PA was not a rare disease but a disease present in more than 10% of all hypertensive patients[7-9] and was resistant to pharmacological treatment. Moreover, it has been demonstrated that hypokalemia is not always present in PA and, in these patients, aldosteronemia or aldosteronuria might be normal or elevated. Furthermore, it has been demonstrated that autonomic hypersecretion of aldosterone is not present in all patients, and its degree turned out to be dependent on salt consumption, body position, and use of some pharmeutical agents (such as oral contraceptives, antidepressants). When considering the heterogeneity of adrenal morphological changes observed in patients with PA and unstable biomarkers of this syndrome, numerous algorithms to confirm or exclude this type of pathology have been proposed recently. First of all, it is recommended to assess aldosteronemia and PRA (under constant conditions of salt consumption and body position). Then it is recommended to calculate the quotient of serum aldosterone levels (ng/dl) and PRA (ng/ml/h/) (A/PRA ratio). If the A/PRA ratio exceeds 60 (if the aldosterone level is expressed as ng/dl) or exceeds 830 (if aldosteronemia is expressed as pmol/l) and serum aldosterone levels exceed 440 pmol/l (>14.5 ng/dl) and PRA is less than 0.5 ng/ml/h,[7] it is recommended

to perform tests to confirm or exclude PA (a sodium chloride load test, captopril test, fludrocortisone or furosemide load test). Finally, it is recommended to determine the levels of aldosterone and cortisol in the venous blood of the adrenals to determine the location of the adrenal gland that accounts for excessive aldosterone secretion. Unfortunately, none of these diagnostic tests has 100% diagnostic reliability.[10] In addition, they constitute additional physical, mental, and financial burden to patients. Therefore, Kaplan[10] suggests to perform extensive diagnostic work-up for PA only in patients with hypertension resistant to pharmacological treatment that manifests with spontaneous hypokalemia and/or incidentaloma.

Recently, interesting links associated with aldosterone production in patients with aldosteronoma have been detected. A mutation of the *KCNJ* gene coding the GIRKA (Kir 3, 4) potassium channel has been reported. Two activating mutations located closely to the selectivity filter of KCNJ5 have been found in 40% of the patients with aldosteronoma. Moreover, 2 syndromes of hereditary arterial hypertension have been identified in patients in whom a G151E mutation with normal zona glomerulosa or a T158A mutation with zona glomerulosa hypertrophy were observed. It has been recently proved that mutation of the KCNJ5 channel is responsible for proliferation and increased sodium permeability, resulting in cell depolarization and calcium influx through the voltage-gated calcium channels.[11,12]

The above discoveries indicate that the pathogenesis of PA is complex, which has a number of important diagnostic and therapeutic implications.

It is extremely important to differentiate between PA and low-renin primary hypertension.[7] A number of papers have reported that low-renin primary hypertension is observed in 20% to 30% of the patients with arterial hypertension.[8,13] PA is considered to be a continuum of low-renin hypertension (LRH).[7]

Epidemiology of primary aldosteronism Considering the lack of unanimous criteria for the diagnosis of PA, the significant differences with regard to its reported prevalence among hypertensive patients are not surprising. In the 1950s, the prevalence of PA among hypertensive patients was assessed to be several percent.[6,8,9] However, when the diagnostic criteria were developed to include also the renin activity test and numerous suppression or stimulation tests, aldosterone secretion tests, assessment of the aldosterone–renin ratio, levels of aldosterone and cortisol in the venous blood of the adrenal glands as well as modern imaging techniques of the adrenal glands, this rate has increased to 10% and more.[4,6,9,14,15] After much controversy,[10,13] scientists finally reached an agreement[13] that the prevalence of PA is from 5% to 15% among patients with arterial hypertension. According to Kaplan,[10] who is an expert in arterial hypertension, there is not enough evidence to consider PA as an epidemic.

Treatment of primary aldosteronism Until recently, there has been a recommendation that aldosterone adenomas should be treated surgically (using laparoscopic adrenalectomy) whereas PA caused by zona glomerulosa hypertrophy with conservative treatment, including aldosterone antagonists (spironolactone, eplerenone). When the paper by Ori et al.[16] was published, treatment of PA, regardless of whether it was caused by an adenoma or zona glomerulosa hypertrophy, should be treated on a long-term basis with low doses of aldosterone antagonists (medium doses of spironolactone, ~37 mg/d, or eplerenone, 50 mg). The authors studied 2 groups of patients. The first group consisted of 24 patients with high aldosteronemia, low PRA, and high A/PRA ratio, while the other included patients with normal aldosterone levels, low PRA, and increased A/PRA ratio. After a 3-year therapy with aldosterone antagonists, both groups of patients had similar regression of the left ventricular hypertrophy and of other biomarkers of cardiac injury. Only in 7 of 48 patients, hypokalemia of less than 3.6 mmol/l was observed. In both groups, systolic and diastolic pressure as well as albuminuria significantly declined. The paper by Ori et al.[16] was reviewed in detail by Funder,[7] who presented the following conclusions in his summary:

1 The incidence of hypokalemia in patients with PA may be even less than 25% to 30% of the patients.

2 In patients with LRH, a similar therapeutic response is observed after therapy with aldosterone blockers as in PA (according to Funder,[7] PA is a continuum of LRH).

3 Patients with PA and LRH have varied sensitivity to the activity of aldosterone inhibitors, which may be caused by the effects of different factors on the synthesis of aldosterone and on the sensitivity of its receptors. Thus, it is exceptionally difficult to determine the so called reference range for aldosteronemia and PRA.

4 Patients with PA constitute approximately 30% of all hypertensive patients, and 20% of the patients in this group have LRH with normal aldosteronemia and an increased A/PRA ratio.

5 Long-term therapy with low-dose aldosterone antagonists does not result in severe hyperkalemia even when patients are additionally treated with angiotensin-converting enzyme inhibitors or angiotensin type 1 receptor blockers, or exhibit a moderate reduction in estimated glomerular filtration rate.

6 Administration of high-dose MR blockers should no longer be routinely administered and, in the majority of the patients, the spironolactone dose should not exceed 50 mg/d (in 50% of the patients treated with spironolactone, the dose was 25 mg/d or even less).

7 The 2008 guidelines[17] on the diagnosis and treatment of PA have to be updated.

It cannot be excluded that an aldosterone synthesis inhibitor, LCI699, will be a drug of choice in the treatment of PA in the near future.[18]

Critical opinions regarding surgical treatment of PA have been recently expressed by Kaplan[10] and Funder.[7] They pointed to low efficacy of surgical treatment of hypertension (42%)[19] caused by unilateral aldosterone hypersecretion, high incidence of bilateral zona glomerulosa hypertrophy as the reason for PA (present in approximately 70% of the patients with PA, and, additionally, surgical treatment of this form of PA is contraindicated), extremely complex diagnostic procedures associated with numerous traps and high costs, low incidence of side effects associated with the use of low doses of aldosterone blockers,[16] and low likelihood of dangerous hyperkalemia.[7]

Considering all of the above, there are justified doubts whether complex diagnostic procedures should be performed in a substantial number of patients with arterial hypertension, suspected to have PA, who could be successfully treated with MR blockers.[10] These doubts should be solved by randomized clinical trials that comprise a large group of patients with PA subjected to various diagnostic and therapeutic procedures. However, it cannot be excluded that the treatment of choice, especially for unilateral forms of PA, would remain surgical resection of the pathological tissue that is responsible for autonomic hypersecretion of aldosterone. Finally, search for biomarkers specific for the particular morphological types of PA could be of diagnostic and therapeutic relevance.

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ARTYKUŁ POGLĄDOWY

Pierwotny aldosteronizm: nowe spojrzenie na patogenezę, diagnostykę i leczenie u chorych z nadciśnieniem tętniczym

Lidia Hyla-Klekot[1], Franciszek Kokot[2]

1 Chorzowskie Centrum Pediatrii i Onkologii, Chorzów
2 Katedra i Klinika Nefrologii, Endokrynologii i Chorób Przemiany Materii, Śląski Uniwersytet Medyczny w Katowicach, Katowice

SŁOWA KLUCZOWE

chorobowość, diagnostyka, leczenie, pierwotny aldosteronizm

STRESZCZENIE

Pierwotny aldosteronizm (PA) wydaje się patogenetycznie niejednolitą jednostką chorobową. Przypuszcza się, że jednostka ta obejmuje około 30% chorych na nadciśnienie tętnicze. Występująca u tych chorych nieadekwatna, autonomiczna nadprodukcja aldosteronu może być spowodowana gruczolakiem aldosteronowym, przerostem warstwy kłębkowatej, defektami genetycznymi kanału potasowego KCNJ5 lub innymi rzadkimi czynnikami patogennymi. Wbrew dawniejszym poglądom PA może być przyczyną opornego na leczenie, a nie łagodnego nadciśnienia tętniczego, natomiast u 70% chorych stwierdza się nie hipokaliemię (dawniej uważaną za klasyczny objaw PA), lecz prawidłowe stężenie potasu w osoczu. Uważa się, że nadciśnienie niskoreninowe przebiegające ze zwiększoną lub prawidłową aldosteronemią (A), małą aktywnością reninową (*plasma renin activity* – PRA) i podwyższonym ilorazem A/PRA wymaga przeprowadzenia pogłębionej diagnostyki w kierunku PA. Sugeruje się, że PA jest *continuum* nadciśnienia tętniczego niskoreninowego. Za leczenie z wyboru PA sugeruje się długotrwałe podawanie w małych dawkach antagonistów receptora mineralokortykoidowego (spironolaktonu lub eplerenonu), a w przyszłości najpewniej blokerów syntazy aldosteronu (np. LCI699) i to niezależnie od postaci morfologicznej PA. Nie wiadomo jeszcze, czy leczenie farmakologiczne całkowicie wyprze leczenie chirurgiczne niektórych postaci PA. Długotrwałe podawanie antagonistów aldosteronu w małych dawkach jest często niedocenionym, skutecznym leczeniem przeciwnadciśnieniowym; bardzo rzadko staje się ono przyczyną groźnej hiperkaliemii, jeżeli czynność nerek nie jest upośledzona.

Adres do korespondencji:
prof. dr hab. med. Franciszek Kokot, Katedra i Klinika Nefrologii, Endokrynologii i Chorób Przemiany Materii, ul. Francuska 20, 40-027 Katowice, tel./fax: 32-259-14-20, e-mail: fkokot@spskm.katowice.pl
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