Primary aldosteronism – the expanding spectrum of unsolved practical issues

Pierwotny hiperaldosteronizm – coraz większe spektrum nierozwiązanych praktycznych problemów

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KEYWORDS:

- primary aldosteronism
- low-renin hypertension
- aldosterone-to-renin ratio

ABSTRACT

Primary aldosteronism is the most frequent cause of hormonal hypertension. Recent findings support the concept of continuous spectrum of autonomous aldosterone secretion with mild or subclinical forms being even more common than was suspected. Assumptions emerge that a considerable number of low-renin hypertensives might actually have aldosterone overproduction. However, the awareness of the disease and its consequences is still unsatisfactory. Nowadays experts are still trying to manage some unanswered questions and on-going debate on who should be screened for primary aldosteronism and how to do so.

SŁOWA KLUCZOWE:

- pierwotny hiperaldosteronizm
- nadciśnienie tętnicze niskoreninowe
- wskaźnik aldosteronowo-reninowy

STRESZCZENIE

Pierwotny hiperaldosteronizm jest najczęstszą przyczyną nadciśnienia hormonozależnego. Niedawne odkrycia wspierają koncepcję ciągłego spektrum autonomicznego wydzielania aldosteronu, z łagodnymi czy subklinicznymi jego formami występującymi częściej niż podejrzewano. Podejrzewa się, że nadciśnienie niskoreninowe u znacznej liczby pacjentów wynika właśnie z nadprodukcji aldosteronu. Jednakże, świadomość występowania tego schorzenia i jego konsekwencji jest wciąż niezadowalająca. Aktualnie żywa jest debata nad rozwiązaniem wielu problematycznych kwestii oraz nad udzieleniem odpowiedzi na pytania kto powinien być diagnozowany w kierunku pierwotnego hiperaldosteronizmu i jak to robić.

Introduction

Primary aldosteronism (PA) defines the group of disorders, in which aldosterone production is inappropriate for sodium status. Its secretion is relatively autonomous and elevated regardless of renin inhibition and potassium loss. It is also independent of sodium supply and the lack of suppression by sodium loading serves as a key diagnostic criterium. The consequences are deleterious with volume expansion, blood pressure increase and an escalating risk of cardiovascular complications.

Hypertension is regarded as one of the most frequent cardiac disorder. About 10-20% hypertensives have secondary hypertension and some elderly may have both forms, primary and secondary, overlapping and masking each other (1). Primary aldosteronism is now considered as the commonest form of endocrine hypertension (2), with approximately 10% of unselected hypertensives affected (3).

Is it time to screen all patients for primary aldosteronism?

Until the 1990s, primary aldosteronism seemed to be considered as a rare form of hormonal hypertension. On the contrary to this traditional (or historical) belief, primary aldosteronism (PA) is neither infrequent, nor absolutely associated with severe blood pressure elevation or deep hypokalemia.

Recognizing hypertension as one of the most important metabolic and cardiovascular risk factors (4), with approximately billion adults worldwide afflicted, the need for better monitoring and treatment of this disease is well understood. The results of SPRINT survey suggested that high risk patients may benefit from targeting lower systolic blood pressure of less than 120 mm Hg when compared to standard limit of less than 140 mm Hg (5). Going along this track, in United States current American College of Cardiology/American Heart Association practice guidelines defines hypertension as blood pressure more than 130 and/or 80 mm Hg (6). European and the newest 2019 Polish recommendations leave the definition of hypertension mainly unchanged with blood pressure more than 140 and/or 90 mm Hg being the indication for treatment (7-9). Beyond the academic debate on definitions and treatment targets is the reality that even with actual number of hypertensives, many of them still do not meet even the mildest criteria for blood pressure control. One reason for that is the therapy ill-suited for patients with unrecognized secondary hypertension, including primary aldosteronism. According to current guidelines, approximately 50% of hypertensives should be

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screened with aldosterone-to-renin ratio (ARR) as the most reliable tool (10). The newest guidelines validate the use of one measurement of simultaneous aldosterone and renin concentrations in the upright position (at least 2 hours out of bed) that enables broad ambulatory screening. However, in practice the screening in Europe is very limited. The relationship between the severity of hypertension and the prevalence of primary aldosteronism is well documented (11). Therefore Endocrine Society guidelines exclude I stage hypertensives, in whom the prevalence is the lowest, from routine screening unless additional risk factors (hypokalemia or adrenal mass, for example) are present (10). However, mild, subclinical or normotensive (12-14) forms of primary aldosteronism are nowadays more and more often recognized with a lot of chaos regarding what they actually stand for. Recent studies on pathogenesis of primary aldosteronism upgraded the spectrum of primary aldosteronism to these forms with broadly-defined autonomous aldosterone secretion. In cases like that, often young and otherwise healthy, low spontaneous baseline blood pressure prevents from developing hypertension despite aldosterone overproduction. In such cases natriuretic and potassium-sparing mechanisms most likely compensate aldosterone-induced potassium wasting and volume expansion and mask its hemodynamic effects. The conditions that cause vasodilation or sodium-wasting, like genetically preconditioned poor response to vasoconstrictors (like angiotensin II) or even partial mineralocorticoid resistance, contribute to this phenomenon. Female sex hormones, low sodium intake or low body mass index also favor the maintenance of normotension. Thus, some authors suggest screening not only hypertensive, but also normotensive patients with hypokalemia, adrenal incidentaloma, as well as those with borderline elevated blood pressure and the patients who had very low BP levels in the past, but it has recently increased substantially (but still are normotensive) (15).

Thus, some very appalling issues arise with the new concepts of primary aldosteronism. With many not unravelled doubts on how aldosterone excess influence cardiovascular risk on each stage and each form of its spectrum, we may need more experience to exclude mildly-affected patients from screening them. Therefore, who should nowadays be screened for primary aldosteronism is one of the most important, though still unanswered, question. As long as screening hypertensives stays the core of the debate, the normotensive patients are for now far out of the discussion.

The approach to screen all hypertensives with ARR has many advocates (16). Not common in official documents, it was accepted by the Japanese Endocrine Society (17) and explained with the high prevalence of cardiovascular disease and the current low case-detection rate. The uptake of Endocrine Society guidelines in Europe is most probably unsatisfactory as well. Data obtained from general practitioners in Germany and Italy showed very poor awareness of primary aldosteronism and consequently low screening rates in the years 2013-2014 (18). From about 30% of hypertensive patients that should be screened according to previously binding guidelines from 2008, only 7-8% have their ARR calculated with 1-2% of patients being eventually diagnosed with primary aldosteronism – the numbers very disappointing in the population with mean blood pressure at the level of 167-170 / 97-99 mm Hg . Regrettably, we might assume the same situation exists in Poland. The recognition of primary aldosteronism is therefore mainly limited to specialty outpatient clinics and tertiary specialistic departments. Although active screening in all groups at risk in such centers is the experts' very reasonable proposition, it is unworkable with the current numbers of specialists in Poland. What is more, most patients referred to specialty centers would certainly be already treated while waiting for admission. Thus, withdrawing of the medications would be necessary and time-consuming. Screening of newly diagnosed hypertensives allows to omit problems with interpreting ARR values in yet treated patients or modifying once introduced therapy. Still, in the German-Italian study mentioned above (18) only 3% of patients were hormonally assessed prior to therapy introduction. Although it has been several years from this survey, nowadays it seems as much improbable, at least in Poland, that wide screening for primary aldosteronism could take place in primary care or general practices where hypertensives are first diagnosed. When considering ambulatory specialistic care, the screening should be performed whenever possible. The authors, however, point also to the rising costs of broad testing with the consequent further diagnostic proceedings. Thus, the possibility to arrest some patients at the level of ARR should be emphasized (10). The hypertensives with moderate disease, normokalemia, modestly elevated ARR and no information about unilateral lesion raising the suspicion of aldosteronoma in abdominal imaging, could in some cases only be monitored with low-dose mineralocorticoid receptor antagonist's (MRA's) addition to therapy, especially if they are unwilling or unable to proceed.

Bilateral primary aldosteronism still idiopathic or not?

For the last several years, the introduction of new-generation sequencing has improved the understanding of the molecular and genetic basis of sporadic primary aldosteronism (19, 20). The questions are at least two. How the excessive renin-independent production of aldosterone is triggered is the first one. Somatic mutations in ion-channels/pumps-encoding genes involved in aldosterone secretion were discovered in the majority of aldosteronomas (APAs). The most frequent ones (30-40%) are mutations in KCNJ5 gene, a component of the Kir 3.4 potassium channel. Less commonly, mutations occur in genes encoding calcium channels (CACNA1D, CACNA1H), the chloride channel (CLCN2) and the sodium (ATP1A1) and calcium (ATP2B3) ATPases. These different mutations directly or indirectly increase intracellular calcium influx, leading to increased expression and activity of the CYP11B2 enzyme and thus excessive aldosterone production. However, their effect on cell proliferation is variable, calling into question the role of these mutations in adenoma formation, which is the second issue in the development of PA.

The pathogenesis of bilateral adrenal hyperplasia (BAH), and especially CT-negative idiopathic hyperaldosteronism (IHA), is still poorly elucidated. Adrenal macro- or micronodular hyperplasia is not always present in histological examinations. Adrenal specimens derived from normotensive kidney donors, autopsy or adrenalectomy of APAs and rare cases of surgically treated BAH have been evaluated and imunohistochemical stainings have revealed the areas of adrenocorticoid cells with high intensity of aldosterone synthase (CYP11B2), named aldosterone-producing cell clusters (APCCs). These cells carry mutations in genes known from APAs studies (but not exactly the same mutations) (21). Increased autonomous aldosterone production in APCCs has been found to be driven by somatic mutations

in CACNA1D gene. As mentioned above, APAs are mainly caused by mutations in KCNJ5 gene, and in CACNA1D only in 8-10% cases. KCNJ5 mutations are hardly ever seen in APCCs, whereas CACNA1D mutations can result both in APAs or APCCs. The evidence for the role of calcium homeostasis dysregulation in aldosterone overproduction was the basis for the potential therapeutic use of calcium channel blockers in PA. This might be beneficial mainly in MRA refractory, CT-negative PA patients. However, the effective concentrations of actually known L-type calcium channel blocker, nifedipine, seem very high, so more potent drugs are probably necessary(22, 23).

APPCs are also encountered in normotensive patients. The relation between APCCs and age is also well established. Although the hypothesis that APCCs display the zones of autonomous aldosterone production is very strong, it is still not completely clear whether, why or how they progress to overt bilateral or unilateral primary aldosteronism over time in some patients. Recently, the existence of other lesions – APCC-to-APA transitional lesions (AATLs in short), containing APCC-like and micro-APA-like structures – was suggested (24, 25). This might support the hypothesis that APCCs are the initial lesions and APAs originate from these areas (the second-hit mutation may be the reason for this transition). The study by Hayashi et al. associates the presence of APCCs and AATLs with longevity, with the conclusion that the decrease in aldosterone production might have survival advantages (26). Despite the great progress, further studies are needed for better understanding of the discoveries that for now have shaken up of our notion of primary aldosteronism classification and pathogenesis (22).

In addition to genetics of IHA, it is very interesting how metabolic factors interplay with hormone levels. Recent study by JPAS Group on the cohort of 516 APA and 1015 IHA patients suggests the link between bilateral hyperaldosteronism and obesity (27). The authors hypothesize that obesity induces the production of adipocytokines, such as leptin or resistin, which stimulate aldosterone secretion independently of renin levels. In turn, aldosterone promotes obesity via mineralocorticoid receptors that cause adipose cells maturation, creating a vicious cycle. Additionally, obesity stimulates renin-angiotensin system through activation of sympathetic nervous system. This phenomenon counteracts renin decrease as the result of aldosterone overproduction by adrenals. Depending of the intensity of these processes, ARR may increase whenever the latter exceeds. However, further prospective studies are necessary to evaluate changes of ARR with weight gain and reduction to support this hypothesis.

Subclinical primary aldosteronism or low-renin hypertension – all routes come to aldosterone?

Many experts' commentaries as well as the results of recent studies support the notion of continuous spectrum of renin-angiotensin-aldosterone system. Thus, the decisions on cut-offs separating essential hypertension (EH) from primary aldosteronism are in fact only more or less arbitrary. Making an analogy to other hormones, like for example another adrenal hormone cortisol, it is absolutely no surprise that subclinical (or possibly autonomous) aldosterone excess would exist. What's more interesting, it is now well documented that the secretion of both hormones, aldosterone and cortisol, is present in some patients with primary aldosteronism [4-16% (28)]. Although it might be expected that this situation results in worsening of metabolic parameters and cardiovascular risk, the consequences of aldosterone-cortisol co-secretion are yet only partially elucidated (29, 30).

Fortunately, with the time passing by, the historical belief that hypokalemia is a sine qua non condition for primary aldosteronism suspicion has mostly walked away into the oblivion. On the contrary, as mentioned earlier, the presence of hypertension is still prerequisite for screening (10). Studies on normotensives and cases both of familiar and sporadic, unilateral or bilateral PA, are contradicting this conception (31-33). In the study of Brown et al., 850 untreated normotensives were analyzed (34). Patients with suppressed renin concentrations and those with elevated aldosterone (in the context of low-renin) had greater risk of developing hypertension and starting antihypertensive therapy in the future. This finding suggests the clinical relevance of low-renin status even in normotension, not mentioning prehypertensive or hypertensive states.

The trials to divide population with hypertension into groups with similar pathogenic phenotypes and modes of treatment have been going on for years. The term "low-renin hypertension" (LRH) pictures a phenotype with volume expansion being the prevalent pathogenic mechanism. Renal sodium retention, high sodium intake, the presence of MR (mineralocorticoid-receptor)-agonistic agents and genetic predispositions have been listed as presumed causes of volume overload. Low-renin hypertension was historically considered rather a benign form of hypertension (35). However, conflicting data concerning cardiovascular risk profile of LRH patients have been reported. LRH is traditionally defined by plasma renin activity (PRA) radioimmunoassay values less than 1 ng/ml/h (direct renin concentration, DRC, less than aprox. 12-15 mU/l). It accounts for one third of all hypertensives and should be considered as a heterogenic disorder with possible causes depending on the simultaneous aldosterone status (35, 36). In patients with low-renin status and normal-high aldosterone, the contribution of subclinical/mild primary aldosteronism is highly suspected. Recent considerations and insights into the mechanisms of early-stage aldosterone hypersecretion (the discovery of APCC and pAATLs) support the hypothesis that some of these patients may manifest less evident forms of primary aldosteronism. In the study of Luo et al., low-renin hypertensive patients with serum aldosterone more or equal to 9 ng/dl and positive ARR screening value were tested with saline-infusion (in recumbent position) (36). Patients with post-SIT aldosterone value more than 5 ng/dl were diagnosed with undetermined/mild primary aldosteronism and those with aldosterone more than 10 ng/dl with overt primary aldosteronism. So-defined mild form of primary aldosteronism was present in 35,3% low-renin hypertensives. Overt primary aldosteronism was diagnosed in 21% of them. Overall 56,3% of low-renin hypertensives were diagnosed with some form of primary aldosteronism. From patients that agreed to adrenal venous sampling (AVS), 36,2% with overt primary aldosteronism and as much as 29,9% with mild primary aldosteronism had unilateral disease and were subjects to adrenalectomy. In conclusion, the authors state that primary aldosteronism is common in low-renin hypertension and should be recognized and properly treated, not only with medications. However, still many questions exists. The analysis of patients data from this particular study raises doubts whether this "mild" form of primary aldosteronism really represents its early stages, because patients were neither younger nor the duration of hypertension was shorter than in "overt" patients. Thus, further studies are needed

to address these doubts. With the introduction of new seated saline-infusion test that has recently gained popularity in Poland and its cut-off of post-SIT aldosterone more than 6 ng/dl, the question of what is subclinical and what is overt are still left unanswered (37).

Is hypokalemia still a significant finding?

Although normokalemic hypertension emerges now to be the most common phenotype of primary aldosteronism, the presence of low potassium status is still an important indicator of such diagnosis and outcome. Very interesting new data come from the analysis of tertiary hypertension units' patients (38). The study shows that hypokalemia is present in a substantial number of hypertensives – 15,8% if termed as potassium level below 3,7 mmol/l or 8,1% when using 3,5 mmol/l as the cut-off value. The prevalence of primary aldosteronism in hypokalemic patients was 28,1% versus 4,3% in the whole cohort of hypertensives. Spontaneous hypokalemia was indicative for primary aldosteronism in 37,4% of patients, whereas patients with diuretic-induced hypokalemia were diagnosed with PA in 16,5%. The presence of hypertension and potassium level below 2,5 mmol/l resulted in the final diagnosis of primary aldosteronism in as many as 76,7% hypertensives (88,5% if considering only patients with spontaneous hypokalemia). The percentages were gradually decreasing with the increase in potassium level. What's interesting, even 0,8% of patients with kalemia between 5,0-5,2 had primary aldosteronism, so this finding is not preclusive. Primary aldosteronism and hypokalemia were independently associated with the incidence of cardiovascular events, like sustained arrhytmias, coronary heart disease, heart failure decompensation and stroke (38).

Moreover, the presence of hypokalemia may not only predict the diagnosis of primary aldosteronism and higher cardiovascular risk, but also the outcome of subtype diagnosis if PA is confirmed. Hypokalemic primary aldosteronism patients manifest lateralization in aldosterone production in adrenal venous sampling more frequenly than normokalemic subjects (60% versus only 11,5%) (39).

To conclude, hypokalemia is in fact a very important finding. No clear data show prevalence of primary aldosteronism in normotensive hypokalemic patients (40). In some individuals, especially young females (41), in whom the compensatory mechanisms successfully prevent against hypertension, potassium wasting is present (33). The awareness of such situation should prompt assessment of renin-angiotensin-aldosterone profile of these patients, thus also unravelling some other than primary aldosteronism possible causes of hypokalemia.

Diagnostic work-up for primary aldosteronism – withdraw or do not withdraw?

With so many theories of who should be screened for primary aldosteronism, the clue is that the patients would actually be screened in practice. Among the reasons why primary aldosteronism screening is so rarely performed, is the complexity of the procedure and uncertainty about interpreting the results (42). Endocrine Society guidelines feature a long list of necessary preparations and requirements before measuring aldosterone and renin for ARR (which is an easy and cheap test in itself), not mentioning confirmatory testing (10). The so-called "standard" testing conditions means for example the only use of alfa-blockers, verapamil and moxonidine (43) and withdrawal of other antihypertensive drugs. Both doxazosin and verapamil are variously tolerated and have side effects (including ortostatic hypotension and the risk of syncope). Moxonidine is very rarely used in Poland. Some previous data from German Conn's Registry, in which also Polish patients have been enrolled, showed that in as many as half of the patients the withdrawal of interfering medications was not possible (44). In the remaining, the risk of cardiovascular and cerebral events was increased while modifying therapy. However, recent opinions from the same experts are more optimistic (45). According to them, the appropriate exclusion of high risk patients allows to reduce serious adverse effects during therapy adjustment and results in even more than 90% of patients screened in standardized conditions. However, are these conditions really standardized so strictly and from the beginning? Recently, Heinrich et al. confessed to performing initial screening for ARR with the patients receiving their usual medications which seems a very sensible option (46). The withdrawal of medications in high risk patients was scheduled as follows: betablockers, ACE inhibitors, angiotensin II receptor blockers, calcium blockers and low-dose thiazydes were terminated at least one week prior to testing, while loop diuretics and MR antagonists – at least 4 weeks prior to testing (46, 47). These rules are slightly different from current ES recommendations where longer periods of withdrawal are recommended for most antihypertensives (10). In the study discussed above, the mean period of adjustment phase was in fact 9,2 days. What's more, 16,5% of patients were allowed taking amlodipine which is regarded as more neutral than other drugs (48, 49). Side effects were present in almost 20% of cases, mainly palpitations, edema and headaches, hypertensive and hypotensive episodes, but did not end up in the termination of adjustment phase. As expected, especially males with higher systolic blood pressure and more intensively treated hypertension were most likely to develop complications. The study also assessed the safety of confirmatory testing. The authors concluded that captopril challenge test was safer than saline infusion test and should be considered in first place for diagnosing severely hypertensive patients.

A very recent article by Gurgenci et co-authors (50) comes with some similar, alleviated propositions about diagnostic work-up. The authors group drugs in three categories. According to their classification, all diuretics "must be replaced". However, there are as always exceptions to this rule. Even subjects on spironolactone therapy might in rare cases be diagnosed without changes in medications. A patient with clear clinical manifestation on optimally recent MRA treatment presenting renin suppression and elevated aldosterone concentrations would not need any further laboratory exploration. This goes along with the data that the lack of renin rebound during MRA therapy is most likely associated with severe, biochemically evident phenotypes of primary aldosteronism (51). Another class of drugs in Gurgenci's classification gather most popular interfering medications that should be "replaced wherever possible". These are: ACE inhibitors, angiotensin II receptor blockers and, unexpectedly, calcium blockers [the negligible influence of amlodipine on renin-angiotensin-aldosterone system was suggested in some studies (48, 49)]. It is thus quite surprising that precisely only beta-blockers are placed in the third group that might be replaced "in the last move" (52, 53). It could be explained by the fact that simultaneously with renin decrease, aldosterone concentrations fall down

during beta-blocking therapy. Aldosterone level less than 10 ng/dl makes the diagnosis less probable even when ARR is positive. The knowledge about how different drugs influence hormone levels can be very helpful in cases when withdrawing certain drugs is not feasible (like for example stopping betablockers in atrial fibrillation) and was discussed in details elsewhere (54). However, the problematic issue is the accurate knowledge about the medications patients are taking. The pilot study by Sandbaumhuter et al. illustrates very poor adherence to prescribed therapy as 33% of patients were having plasma drug results different from the preconceived (55). That may lead to mistakes while interpreting ARR in accordance to medications' influence on hormone levels if we do not discuss this matter very carefully with the patient. The other issue discussed broadly for the past several years is the ARR cut-off value, both in standardized conditions and when on multidrug therapy. Gurgenci et al. suggest a lower cut-off for ARR than officially recommended – 70 pmol/l/mU/L comparing to 91-122 pmol/l/mU/L in ES guidelines (10). This is not the first time that the lower ARR cut-off when screening patients taking their antihypertensive medications is proposed (49, 56). Possibly, not the exact values, but taking into account the whole clinical situation of the certain person can let us make the right decisions about further proceedings ensuing ARR, including close monitoring of the patients with negative or undetermined values but high risk of primary aldosteronism.

To sum up, independently of these problems still present in the dynamic field of primary aldosteronism, the progress in diagnosing these patients is optimistically going on. According to already mentioned German Conn's Registry, the tendency towards milder forms being diagnosed due to more intensive screening was seen yet in the years 2014-2016. More patients with bilateral disease with higher kalemia levels were diagnosed and so properly treated pharmacologically. In the same time, younger and female patients known to have higher prevalence of surgically treated unilateral disease with better post-operative outcomes (57), were recognized.

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