



Problems in diagnostics of primary aldosteronism — analysis of the own data

Trudności diagnostyki pierwotnego aldosteronizmu — analiza materiału własnego

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Abstract

Introduction: During the last few years, increasing evidence suggests that primary aldosteronism is the cause of over 10% of arterial hypertension (AH). There are no “gold standard” methods for PA screening. The aim of study was plasma renin activity (PRA), plasma aldosterone concentration (PAC), and ARR assessment as criteria for diagnosis of PA and their usefulness in clinical practice.

Material and methods: Eighty-one consecutive patients were admitted for diagnosis of primary aldosteronism: 51 women and 30 men, aged 31–69 years. In each patient, PAC and PRA were evaluated by radioimmunoassay. In 65 patients, urine concentration of catecholamine metabolites was assayed, and in 51 patients, diagnostics for hypercortisolemia was carried out. In patients with adrenal incidentaloma, 16-row computer tomography was performed.

Results: The proportion of patients with PAC over 150 pg/ml was 35% ($n = 28$). The number of patients with PRA under 0.07 ng/ml/h was 19 ($n = 15$). The ratio of patients whose values of ARR exceeded over 20, 30, 40, 50, and 180 were 55, 47, 37, 28, and 15%, respectively.

Conclusions: The most common indication for primary screening was the presence of incidentally found adrenal mass. The quotient of plasma aldosterone concentration/plasma renin activity at whichever cut-off point is not effective enough for the selection of patients for further diagnostics or its cessation. (*Pol J Endocrinol* 2010; 61 (1): 2–5)

Key words: aldosterone, renin, hypertension, primary aldosteronism

Streszczenie

Wstęp: W kilku ostatnich latach pojawiła się znaczna liczba doniesień sugerujących, że pierwotny aldosteronizm stanowi przyczynę ponad 10% przypadków nadciśnienia tętniczego (AH, *arterial hypertension*). Nie dysponujemy obecnie metodami skriningowymi pierwotnego aldosteronizmu (PA, *primary aldosteronism*), które można uznać za “złoty standard”. Celem pracy była ocena reninowej aktywności osocza (PRA, *plasma renin activity*), stężenia aldosteronu w osoczu (PAC, *plasma aldosterone concentration*), wskaźnika aldosteron–renina (ARR, *aldosterone–renin ratio*) jako kryteriów rozpoznania PA i określenie ich przydatności w praktyce klinicznej.

Materiał i metody: W badaniu wzięło udział 81 kolejnych pacjentów przyjętych w celu diagnostyki PA: 51 kobiet i 30 mężczyzn w wieku 31–69 lat. U każdego chorego oznaczono PAC i PRA metodą radioimmunologiczną. U 65 pacjentów określono stężenie metabolitów katecholamin w moczu. U 51 przeprowadzono diagnostykę w kierunku hiperkortyzolemii. U pacjentów z *incidentaloma* nadnerczy wykonano 16-rzędową tomografię komputerową.

Wyniki: Odsetek pacjentów z PAC > 150 pg/ml wynosił 35% ($n = 28$), zaś z PRA < 0,07 ng/ml/h 19% ($n = 15$). Wartości ARR przekraczające kolejne punkty odcięcia 20, 30, 40, 50 i 180 stwierdzono u odpowiednio 55, 47, 37, 28 i 15% badanych.

Wnioski: Najczęstszym wskazaniem do skriningu w kierunku pierwotnego aldosteronizmu stanowiła obecność przypadkowo wykrytego guza nadnerczy. Iloraz aldosteronemii do aktywności reninowej osocza, bez względu na przyjęty punkt odcięcia, nie stanowi wystarczającego kryterium, będącego podstawą do prowadzenia dalszej diagnostyki lub jej zaniechania.

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Słowa kluczowe: aldosteron, renina, nadciśnienie, pierwotny aldosteronizm

Introduction

Until recently, primary aldosteronism has been thought a minor cause of arterial hypertension (AH). In recent years an increasing number of cross-sectional and prospective clinical studies have suggested that primary aldosteronism (PA) is the cause of over 10% of AH [1–7]. In the case of forms of AH resistant to antihypertensive

agents, the proportion of patients is higher and reaches 11–22% [4, 5]. Confirmation of PA is the basis of the start of diagnostic investigation for the reason for PA [6, 7]. The means of the treatment — surgical or pharmacological — depends on the recognized cause of PA. The effectiveness of the adrenalectomy depends on early diagnosis and is measured by the proportion of normotensive patients [8]. However, effective treatment by surgery



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or pharmacotherapy is also associated with elimination of the negative influence of increased aldosterone levels on the epithelium, vascular smooth muscles, and in consequence on cardiovascular complications [9, 10]. The above data suggest an important place of screening tests for PA in the diagnostic investigation of AH, especially in several patient groups: young, with severe hypertension, drug-resistant AH, and AH with adrenal incidentaloma and/or with spontaneous or diuretic-induced hypokalaemia [1, 7]. The tests that are presently used — plasma renin activity (PRA) and plasma aldosterone concentration (PAC) — are exposed to high laboratory error, and low sensitivity and specificity. This has led to the use of PAC/PRA quotient (ARR, aldosterone–renin ratio) instead of PRA or PAC separately. Unfortunately, the cut-off values for ARR in many multiple independent studies are different and are still controversial because the range averages from 20 to 100 [1–7, 11]. Taking into account the above data, the objective of the present work was the assessment of PRA, PAC, and ARR as criteria for diagnosis of PA, and their usefulness in clinical practice.

Material and methods

This retrospective study was performed on 81 consecutive patients hospitalized during the years 2006–2008 at the Clinical Department of Endocrinology UMB admitted in order to diagnose primary aldosteronism. This group contained 51 women (63%) aged 57 ± 11.7 years and 30 men (37%) aged 50 ± 19.2 years. In each patient, plasma aldosterone and plasma renin activity, and sodium and potassium plasma concentrations were evaluated. In 65 patients, urine concentration of catecholamine metabolites was assayed, and in 51 patients, diagnostics for hypercortisolaemia was carried out. In patients with adrenal incidentaloma (AI), 16-row computer tomography was performed with description of tissue density in Hounsfield's scale. Before determination of PAC and PRA was performed, the deficiency of potassium was compensated; diuretics and spironolactone were withdrawn for at least 4 weeks, for 2 weeks: β -adrenergic blockers, clonidine, methyl dopa, dihydropyridine calcium channel antagonists, angiotensin — converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs. PAC was determined by radioimmunoassay method with RIAZENco kit ZenTech (Angleur, Belgium). The value of CV was 5.3%, sensitivity 1.4 pg/ml, and specificity 100%. PRA was assayed by radioimmunoassay method with use of REN-CT2 kit of Radim Company (Rome, Italy). The value of the CV test was 7.18%, sensitivity 0.15 ng/ml, and specificity 100%. Determinations of urine metanephrine and normetanephrine were per-

formed by immunoassay method using Nephtrines Urine kits from Biosource (Nivellas, Belgium). Value expectations: metanephrines $< 350 \mu\text{g/day}$; normetanephrines $< 600 \mu\text{g/day}$; Sensitivity: metanephrines 5 ng/ml; normetanephrines 13 ng/ml. CV for metanephrines 5.2%, for normetanephrines 12.2%. Cortisol was evaluated by chemiluminescence method with Architect System kits, Abbott company (Germany, Wiesbaden): sensitivity $\leq 1 \mu\text{g/dl}$, CV 20%.

Results

The indication to assay PRA and PAC was adrenal incidentaloma (AI) in 50 patients (61.7%), drug-resistant hypertension in 16 (19.7%), early-onset hypertension (< 40 years) in 8 (9.9%), hypertension and hypokalaemia in 4 (4.9%), and hypokalaemia without hypertension in 2 (2.5%). Figure 1 shows the prevalence of patients with particular indications to diagnosis of PA (with reference to the whole group; $n = 81$) in which ARR exceeded consecutive cut-offs. The ratio of patients whose values of ARR exceeded over 20, 30, 40, 50, and 180 were 55, 47, 37, 28, and 15%, respectively.

The ratio of patients with plasma aldosterone concentration over 150 pg/ml is shown in Figure 2, and the proportional rate of the patients with plasma renin activity under 0.07 ng/ml/h is illustrated in Figure 3. Figure 4 shows the ratio of patients in which the existence of three criteria helpful in the diagnose of PA were detected: $\text{ARR} > 20$, $\text{PAC} > 150 \text{ pg/ml}$, $\text{PRA} < 0.07 \text{ ng/ml/h}$ ($n = 7$) and the proportional rate of patients that had hypokalaemia apart from the three criteria above ($n = 4$) compared to the whole group ($n = 81$). In the group of the patients in whom $\text{ARR} > 180$ ($n = 12$), in 9 (66.6%) $\text{PAC} > 150 \text{ pg/ml}$ and $\text{PRA} < 0.07 \text{ ng/ml/h}$ was found as well.

Discussion

The most numerous group of patients sent for PA screening in our study was the AI group. The majority of IA patients appeared to have increased percentages of elevated ARR, independently of the cut-off point. The research indicated significantly increased PAC in every third patient (35%) and considerably decreased PRA in every fifth patient (19%). These ratios significantly exceeded the statistical population prevalence of PA as a cause of hypertension. In every tenth of the examined patients (11%), the coexistence of three criteria suggesting PA ($\text{ARR} > 20$, $\text{PAC} > 150 \text{ pg/ml}$ and $\text{PRA} < 0.07 \text{ ng/ml/h}$) were found. This percentage could reflect the population prevalence of PA [1–7]. However, our experience with the saline confirmation test (unpublished data) shows that in some of the patients with all three of the

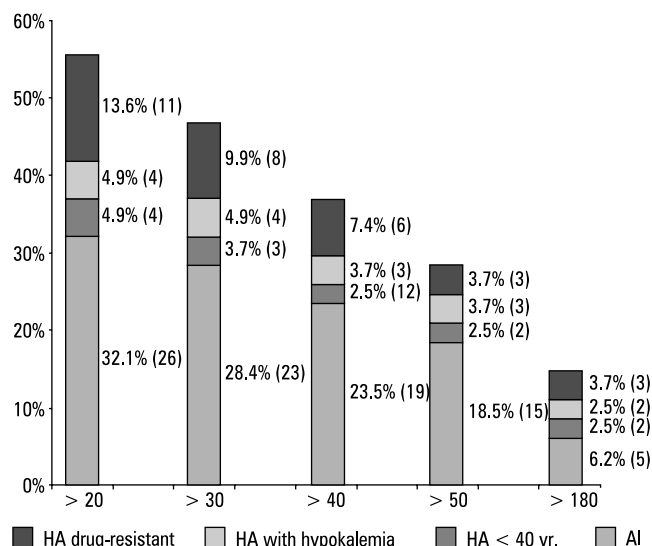
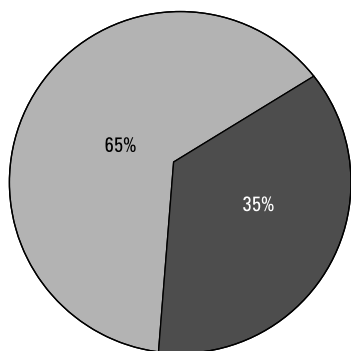


Figure 1. Ratio of patients' particular indications to diagnose primary aldosteronism (in comparison to the whole group; $n = 81$) in which plasma aldosterone to renin ratio exceeded consecutive cut-offs

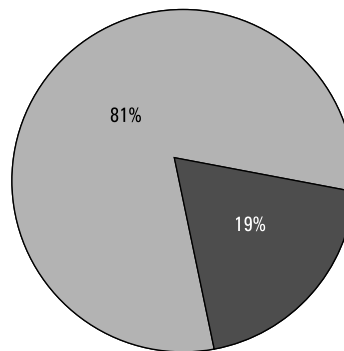
Rycina 1. Procentowe występowanie poszczególnych wskazań do diagnostyki w kierunku pierwotnego aldosteronizmu (w porównaniu z całą grupą $n = 81$) w zależności od wartości odcięcia wskaźnika aldosteron–renina



■ PAC > 150 pg/ml ($n = 28$) □ PAC ≤ 150 pg/ml ($n = 53$)

Figure 2. The rate of the patients with plasma aldosterone concentration over 150 pg/ml

Rycina 2. Odsetek chorych, u których stężenie aldosteronu w osoczu przekraczało 150 pg/ml



■ PRA ≤ 0.07 ng/ml/h ($n = 15$) □ PRA > 0.07 ng/ml/h ($n = 66$)

Figure 3. Proportional rate of patients with plasma renin activity under 0.07 ng/ml/h

Rycina 3. Odsetek chorych, u których reninowa aktywność osocza wynosiła poniżej 0,7 ng/ml/h

above criteria present saline normalise PAC. In the group of patients who fulfilled the three criteria of PA, 4 of the 11 additionally had hypokalaemia, which makes diagnosis of PA more probable. However, hypokalaemia is seen in the minority (9–37%) of PA cases [1–7, 11]. The ratio of patients whose values of ARR exceeded 20, 30, 40, 50, and 180 was 55, 47, 37, 28, and 15%, respectively. However, PAC > 150 pg/ml and PRA < 0.07 ng/ml/h coexisted only in two-thirds of patients with significantly increased ARR > 180. Moreover, even a cut-off value of ARR=180 was exceeded by 15% of the values. On one hand, this data suggests a significant ratio of false positive rates of ARR at whichever ARR cut-off

point, when the statistics of PA in hypertension are taken into account. On the other hand, significantly increased ARR probably does not constitute certain diagnosis of PA. In the PAPY study, positive rates of ARR at a cut-off point of 40 were observed in 20% of AH patients [1]. In our study, 37% of patients had positive rates at this cut-off level. In the study by Nishizaka et al., positive rates were noticed in 69% of cases at ARR = 20 as an optimal (sensitivity and specificity about 80%) [11]. In our analysis, in 55.5% of patients, this criterion was present. It is necessary to take into account the fact that mathematically PRA affects the PAC/PRA ratio to a further degree than PAC, as far as PRA could range from

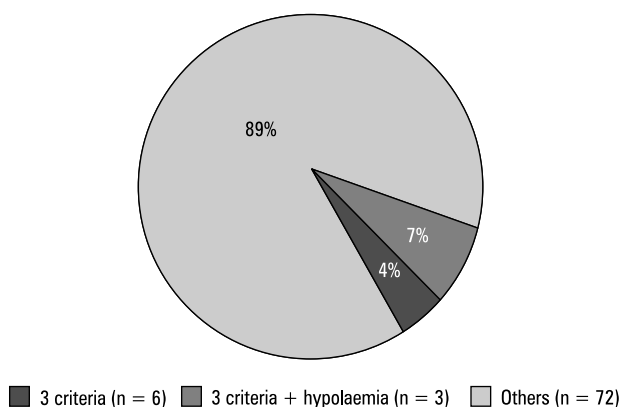


Figure 4. The rate of patients in which 3 criteria helpful to diagnose PA were detected: ARR > 20, PAC > 150 pg/ml, PRA < 0.07 ng/ml/h ($n = 7$) and percentage of the patients with 3 criteria and hypokalaemia ($n = 4$) compared to the whole group ($n = 81$)

Rycina 4. Odsetek chorych, u których stwierdzono 3 kryteria pomocne w rozpoznaniu PA: ARR > 20, PAC > 150 pg/ml, PRA < 0,07 ng/ml/h ($n = 7$) oraz odsetek chorych, u których stwierdzono 3 kryteria i hipokaliemię ($n = 4$) w porównaniu z całą grupą ($n = 81$)

hundredth hundredths to dozens (4 classes of size) and PAC from dozens to several hundred (2 classes of size). Moreover, lower values of PRA are more frequently seen in patients over 65 [7, 12]. To prevent pre-laboratory mistakes in PAC/PRA determination it is necessary to correct the deficiency of potassium, withdraw diuretics and spironolactone for at least 4 weeks, and β -adrenergic blockers, clonidine, methyl dopa, dihydropyridine calcium channel antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs (elevation PAC/PRA) for 2 weeks. ARR should be evaluated in blood samples collected at mid-morning, after the patient has been up for at least 2 hours and seated for 5–15 minutes [6, 7]. Antihypertensive medications of lesser effect on the ARR are verapamil, hydralazine, and β -adrenergic blockers (prazosin, doxazosin, terazosin). Our data suggest the necessity of using confirmatory tests independently of the chosen cut-off points. Confirmation of PA may be obtained by methods that enable verification of the autonomic character of aldosterone secretion: oral or intravenous tests of sodium loading or fludrocortisone [7, 12]. The captopril test is not recommended because of the diverse influence on PAC in the group of patients with adrenal hyperplasia and adrenal adenoma [7]. Early diagnosis of PA caused by unilateral change (majority of PA) and further adrenalectomy (preferable in endoscopic approach) gives the patient a higher chance for normotension without antihypertensive medication. Significant factors of effectiveness of surgical treatment also include age, gender, and tumour size [8, 13, 14].

Waltz et al. observed 40% effectiveness of surgical treatment at patients with ≤ 5 years duration of hypertension *v.* 24% when that time was longer, 42% of effectiveness in a group of patients aged ≤ 50 years *v.* 15% who were elderly and 42% of females *v.* 16% at males [8].

In summary, on one hand, increased availability of diagnostic methods (mainly ultrasonography) that make diagnosis of AI easier, the growing prevalence of hypertension in patients with metabolic syndrome, and the awareness of the more frequent causative role of PA in HA based on recently published studies increases the number of patients sent to be diagnosed for PA. On the other hand, there are no “gold standard” screening tests of satisfactory specificity and sensitivity, which makes PA diagnosis difficult and equivocal.

Conclusions

1. The most common indication for case detection of primary aldosteronism was the presence of incidentally found adrenal gland tumours.
2. The quotient of plasma aldosterone concentration/ plasma renin activity at whichever cut-off point is not effective enough to select patients for further diagnostics.

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