The prevalence of primary aldosteronism (PA) in a group of 350 hypertensive patients

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Summary

Background Hypertension is one of the commonest diseases worldwide. Its prevalence is estimated to approximately 25% of the population. In addition, hypertension is an important risk factor for increased cardiovascular events. In most cases it is of idiopathic origin, but may also be due to another disease, e.g. endocrine dysfunction. Primary aldosteronism (PA) is a common cause of resistant hypertension; its proper diagnosis determines further therapy. The aim of this study was to evaluate the prevalence of PA in a group of 350 patients (240 women and 110 men) with hypertension.

Material and method All patients underwent hormonal tests including assessment of the levels of: ACTH, cortisol (baseline and in dexamethasone suppression test), DHEA-S, chromogranin A, VMA urine excretion, aldosterone and active renin. Afterwards, an intravenous load test with 0.9% neutral saline solution was performed. Abdominal ultrasound was performed in all patients, and abdominal computed tomography only in patients with abnormal hormonal tests. Other forms of secondary hypertension were previously excluded.

Results Primary aldosteronism was diagnosed in 58 patients (16.6%) — 38 women and 20 men. Adrenal adenoma was found in 20 patients (34.5%), and idiopathic hyperaldosteronism in 38 patients (65.5%). Hypokalaemia occurred in 25 patients (43.1%). Moreover, it was found that the aldosterone-renin ratio above 8.25 supports the diagnosis of PA.

Conclusion We conclude that the diagnosis of PA should not be limited only to the hypertensive patient with hypokalaemia. PA is an important cause of hypertension, especially among patients with difficulties in normalization of blood pressure with standard pharmacological treatment.

key words: hypertension, aldosterone, primary hyperaldosteronism

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Background

Hypertension is one of the most frequently diagnosed diseases worldwide. Two large projects started the analysis of the epidemiology of hypertension: the Framingham study population and the Seven Countries Study. The prevalence of high blood pressure was estimated to approximately 25% of the population [1, 2]. The prevalence of hypertension varies depending on the geographical, socio-cultural and economic factors. Some other studies have shown that the incidence of hypertension depends on the age and diet and ranged from 3.4% to 68.9% among men and from 6.8% to 72.5% in women [3, 4]. In the population of Africa and the underdeveloped south of China prevalence of hypertension does not exceed 15%, in Western Europe and the US white population is moderate and around 15–30%, while in Poland, Russia, Finland and among African Americans in the United States is estimated approximately to 30% [5].

The most recent Polish multicentre national project WOBASZ enrolled 13 545 subjects (6392 men

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and 7153 women), aged 20–74 years. The average incidence of hypertension in Poland was about 36%. Hypertension was higher in men (42.1%) than in women (32.9%) [6].

High blood pressure is considered as one of the most important risk factors for cardiovascular events such as coronary artery disease, heart failure and intracerebral stroke. These conditions are the main causes of death, morbidity and disability in Poland, other European countries and the United States [1].

The largest meta-analysis of Lewington [1] and MacMahon [2] showed an increased risk of cardiovascular disease above 115/75 mmHg. Moreover, every 5 mmHg elevation in diastolic blood pressure is related to increased risk of stroke by 34% and coronary artery disease by 21% [2]. According to Lewington *et al.* [1], the rise in systolic blood pressure of 20 mmHg and/ /or diastolic blood pressure of 10 mmHg more than doubles the risk of death from brain stroke, ischaemic heart disease and other vascular causes.

In most cases hypertension is of idiopathic but may also be due to another disease such as renal structure or vascular disturbances or endocrine dysfunction. The main goal of the diagnosis of hypertension is secondary high blood pressure detection because this determines further therapy.

Goal

The aim of this study was to evaluate the prevalence of primary aldosteronism in a group of 350 patients (240 women and 110 men) with hypertension.

Material and methods

All patients underwent hormonal tests including assessment of the levels of: ACTH, cortisol (baseline and in dexamethasone suppression test), DHEA-S, chromogranin A, VMA urine excretion, aldosterone and active renin. Afterwards an intravenous load test with 0.9% neutral saline solution (2.0 l within 4 hours) was performed. The concentration of active renin was measured by radioimmunoassay method and aldosterone by RIA technique. Abdominal ultrasound was performed in all patients, and abdominal computed tomography only among patients with abnormal hormonal tests. Other forms of secondary hypertension were previously excluded.

Results

Primary aldosteronism was diagnosed in 58 patients (16.6%) — 38 women and 20 men. Adrenal adenoma was found in 20 patients (34.5%), and idiopathic hyperaldosteronism in 38 patients (65.5%). Hypokalaemia occurred in 25 patients (43.1%). In addition, it was found that the aldosterone-renin ratio above 8.25 supports the diagnosis of primary aldosteronism. The results suggest that primary aldosteronism seems to be one of the most common causes of secondary hypertension. The dominant group of patients was those with an idiopathic aldosteronism without hypokalaemia. Data were statistically analysed using MS Office Excel and Statistica Software. Data are shown in Table I and II.

Discussion

The history of primary aldosteronism (PA) is not so long and has only 61 years. The first description of coincidence of an adrenal cortical tumour and hypertension was published in 1953 by the Polish doctor

Table I. Characteristic of study group

	n	(%)
Total number of patients, including:	350	100
Women	240	68.6
Men	110	31.4
The number of patients with hyperaldosteronism, including:	58	16.6
Women	38	65.5*
Men	20	34.5*
Hyperaldosteronism form:		
Adenoma	20	34.5*
Idiopathic	38	65.5*
With hypokalaemia	25	43.1*

*for a group of patients with hyperaldosteronism

Table II. Concentration of potassium, aldosterone and active renin

Parameter	Mean ± SD	Range	Normal values
Potassium [mmol/l]	3.75 ± 0.62	2.77–5.22	3.5–5.5
Aldosterone [ng/dl]	77.6 ± 30.54	22.4–180.3	4–31
Active renin [pg/ml]	2.88 ± 2.65	0.0–9.4	3.6–65.6

Michał Lityński [7]. Unfortunately, the results of his work were not complete because of impossibility in determination of the level of aldosterone. Only two years after the Lityński's publication Jerome W. Conn proved that increased secretion of aldosterone by the adrenal zona glomerulosa is responsible for high blood pressure [8].

Most commonly PA is due to bilateral adrenal hyperplasia (BAH) of zona glomerulosa; less frequent is an aldosterone producing adenoma (APA) — classic Conn's syndrome [9]. Other cause of PA are even more rare, such as cancer (about 1%), ectopic secretion of aldosterone (approx. 1%), family aldosteronism (about 1%) or unilateral nodular adrenal hyperplasia (approx. 1%) (the so-called 1% rule) [10]. Recently, in approximately 50% of patients with APA specific genetic alteration have been detected [9].

The incidence of PA among hypertensive patients is usually estimated around 6–13% [11–13]. However, a 10% prevalence of PA was found among hypertensive patients in prospective studies, and this figure raised to around 30% when aldosterone–renin ratio (ARR) was used as a screening test by general practitioner [9].

Gordon *et al.* (1994) in one of the most important reports found PA in 8.5% of 199 patients with normokalaemic hypertension [14].

Eide *et al.* (1996) recognized PA as a cause of high blood pressure in 23% among patients with refractory hypertension [15]. Gallay *et al.* (2001) found PA in a group of 17% patients [16].

The Czech authors [17] analysed cases of secondary hypertension in a group of 402 patients, the most common was PA (19%), while the incidence of pheochromocytoma was 5% and renal-vascular hypertension 4.5%, hypercortisolism and renal disease were less than 3% of diagnoses.

Omura *et al.* (2004) found PA in 6% of Japanese hypertensive patients [18]. The multicentre study involving five continents [19] showed a higher frequency of PA than previously thought. It was found that PA is responsible for 8–14% of cases of hypertension, only 10–37% with hypokalaemia. Adrenal adenoma was found in 10–30% of patients.

Rossi *et al.* (2006) confirmed PA in 11.2% patients, around 6.4% had idiopathic PA; adrenal adenoma was diagnosed only in 4.8% of patients [16].

The RESIST-POL study conducted in the years 2009–2012 in the Department of Hypertension, the Institute of Cardiology, Warsaw, enrolled 204 patients with resistant hypertension. Primary aldosteronism was found in 16% of patients [20].

It is worth to say that after almost 10 years after the description of the "classical" phenotype of primary aldosteronism, Conn estimated that approximately 20% of patients with hypertension may have adrenal adenoma and hyperaldosteronism [21].

In our study, we found that PA is responsible for 16.6% cases of hypertension (more frequent than the average), moreover 65% of PA was of idiopathic origin.

In our study, hypokalaemia occurred only in 23 patients (42%). This finding is consistent with the observations of Conn in 1965 [22] and other authors [23, 24] who presented data where hypokalaemia was found in only 30–40% of patients with PA, and was mostly observed in patients with a single adenoma.

Aldosteronoma was found in only 20–40% of patients with PA. These patients usually presented the classic phenotype of Conn's syndrome including hypertension, hypokalaemia [25, 26]. PA caused by bilateral adrenal hyperplasia is estimated at approximately 60%. In our work the adrenal adenoma was found in 35%.

According to Gordon *et al.* (2007), screening for PA should be performed in all patients with hypertension — including those without hypokalaemia and without positive family history [27]. Delay in diagnosis of PA can lead to irreversible consequences. Incorrect treatment reduces the chance of obtaining normal blood pressure.

The wide variation of the ARR cut-offs complicates the diagnostic criteria and choice of "gold standard" test to definitely confirm or exclude PA. Although determining the rate of ARR is considered to be the most reliable method of screening for PA, its interpretation is complex and requires individual assessment of the impact of various factors that may affect the renin-angiotensin-aldosterone system (RAAS). To reduce the proportion of both false positive rates and false negative, it is essential to eliminate the effects negative factors affecting the RAAS. The estimation specificity of ARR varies from 71–84% with sensitivity ranging from 73% to 93%, whereas the prevalence of PA was found to be 13% [9].

In contrast, Young (1997) suggested that for the initial diagnosis of PA, in addition to the ARR above 20, another necessary criterion is the level of aldosterone higher than 15 ng/dL [28]. This condition of established diagnosis of PA was met in 90% of Mayo Clinic patients with confirmed adrenal adenoma [29].

Some authors found that 47% of patients suffering from PA had ARR above 30 [30] (usually taken as the cut-off level) and 28% of those patients had ARR above 50 [31]. In our study it was found that

the ARR above 8.25 supports the diagnosis of primary aldosteronism. It should be emphasized that we used active renin concentration instead of plasma renin activity.

Conclusion

It is widely known that the prevalence of PA is higher than previously believed. We conclude that the diagnosis of primary aldosteronism should not be limited only to the patient with high blood pressure and hypokalaemia. Primary aldosteronism is an important cause of hypertension, especially among patients with difficulties in normalization of blood pressure with standard pharmacological treatment. Delay in establishing the diagnosis may affect the response to treatment and overall prognosis.

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