

Prevalence of primary aldosteronism among bulgarian hypertensive patients

Research Article

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Abstract: Primary aldosteronism (PA) has long been considered a rare disease, but a higher prevalence was suggested recently. The aim of this study was to evaluate the prevalence of PA in a group of Bulgarian hypertensive patients, including patients with adrenal incidentalomas (AI). The aldosterone to renin ratio (ARR) > 750 was used as a positive screening test and the Captopril test was performed to confirm the diagnosis. Adrenal CT scan was used to differentiate between the main subtypes of PA- aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism (IHA). The diagnosis of APA was retrospectively confirmed after surgery. After excluding other forms of endocrine hypertension, except PA, we investigated a total of 472 consecutive hypertensive patients, among them 96 patients with AI. Final diagnosis of PA was reached in 38 patients (8.05%) in the entire hypertensive population and in 12 patients (12.5%) among hypertensive patients with AI. In the group of PA, 15 patients (39.5%) were diagnosed with APA and 23 patients (60.5%) had an IHA. Among all patients with PA 21 (55.3 %) presented with hypokalemia. Our findings of a relatively high prevalence of PA support an early diagnosis of this potentially curable disease, especially in hypertensive patients with AI.

Keywords: Hypertension • Primary aldosteronism • Prevalence • Aldosterone/ renin ratio

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1. Introduction

Until recently primary aldosteronism (PA) has been considered a rare cause of hypertension [1]. However, a higher prevalence, ranging between 5-20% in some reports, was suggested in the last decade [2]. This could hardly be explained by an increase in the number of affected patients, but it is probably due to a change in the diagnostic approach, resulting in the widespread use of the aldosterone/renin ratio (ARR), the investigation of normokalemic along with hypokalemic hypertensive patients as well as the wider use of adrenal imaging techniques. Actually the estimation of the true rate of PA is still a controversial question raising polemics in the literature [3,4]. Factors, which could influence the prevalence of PA, include different study populations, concomitant use of medications while performing hormonal investigations, different cut-off values for the

ARR or differences in confirmatory tests. The proportion of the two main forms of PA- aldosterone-producing adenoma (APA) or idiopathic hyperaldosteronism (IHA) is also controversial partly depending on factors like the availability of adrenal venous sampling (AVS). Also, it is a still unanswered question, which patients should be screened for PA and if it is worthy to evaluate all hypertensive subjects in view of the cost-benefit ratio. The significance of the problem about the real prevalence of PA is underlined by studies, which reported harmful non-hemodynamic cardiovascular effects of aldosterone [5,6] and a higher number of cardiovascular events in patients with PA [7,8]. These findings are in favor of the increased cardiovascular risk of patients with PA and justify an extensive screening for this disease.

Until now there are no data on the prevalence of PA among hypertensive patients in Bulgaria. The aim of this study was to evaluate the prevalence of PA in a group

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of consecutive hypertensive patients, including patients with adrenal incidentalomas, referred to the Clinical Centre of Endocrinology in Sofia, Bulgaria.

2. Material and Methods

2.1. Study population

The study population consisted of hypertensive patients referred to the Clinic of pituitary and adrenal diseases in the Clinical Centre of Endocrinology in Sofia, which is the reference centre for endocrinology in Bulgaria. Hypertensive patients are referred to this clinical centre for one or more of the following reasons: hypertension resistant to conventional antihypertensive treatment, hypertension associated with spontaneous or diuretic-induced hypokalemia, onset of hypertension at young age, hypertension associated with adrenal incidentaloma, hypertension associated with the metabolic syndrome, paroxysmal hypertension with the suspicion of pheochromocytoma, suspicion of other endocrine causes of hypertension (thyroid dysfunction, Cushing's syndrome, congenital adrenal hyperplasia). For the purpose of this study we screened consecutive patients, who fulfilled the following criteria: (1) 18-80 years of age; (2) confirmed arterial hypertension. Hypertension was confirmed by measuring office blood pressure according to the recommendations of the European Society of Hypertension (ESH) [9] and/or 24-hour ambulatory blood pressure monitoring, or by previous use of antihypertensive medication. The recommendations of the ESH were used for definition and classification of blood pressure levels and hypertension grade [9]. In all hypertensive subjects other secondary forms of hypertension except PA were ruled out by means of complete medical history, physical examination, and appropriate biochemical and hormonal tests and imaging studies. All subjects were studied after signing a written informed consent form according to a protocol approved by the Ethics Committee of the Medical University of Sofia.

2.2. PA diagnosis and subtype differentiation

Prior to blood sampling medications that can interfere with the measurements of aldosterone and renin (beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics) were stopped for at least 7-10 days, and spironolactone for at least 45 days. Alpha-blockers, calcium channel blockers, and centrally acting medicaments (Rilmenidine, Moxonidine) were used for controlling hypertension. Hypokalemia was defined as serum potassium lower than 3.5 mmol/l

and was corrected using potassium supplements when present. All subjects followed their usual diet.

Blood samples for serum aldosterone and plasma renin activity (PRA) were taken between 8-10 h am, after the patient had been sitting for 30 minutes, the ARR was then calculated. In patients with elevated ARR (> 750 pmol/l per ng/ml/h) [10] and aldosterone > 416 pmol/l [2] a confirmatory test (Captopril test) was performed. The diagnosis of PA was confirmed if the ARR was > 970 on the 90-th minute after the oral administration of 50 mg of Captopril, while the patient had been in the sitting position [11]. The subtype differentiation (APA or IHA) was made using imaging studies of the adrenal glands - computed tomography (CT) or magnetic resonance imaging (MRI). When a solitary unilateral adenoma was visualized patients were considered to harbor an APA and were surgically treated (laparoscopic adrenalectomy). The diagnosis of APA was confirmed by histological investigation and a reversal of hypertension and/or hypokalemia during the follow-up. IHA was considered in all patients in which no adrenal mass or nodule was visualized on CT or MRI and they received medical treatment. Patients with an apparent unilateral adenoma on CT/MRI who refused operation were classified as having APA. Adrenal venous sampling (AVS) was not available for the subtype differentiation of PA. In all patients with PA PCR long range was performed using the method described by Jonsson JR *et al* in order to exclude glucocorticoid-suppressible hyperaldosteronism [12].

2.3. Laboratory assays

Serum aldosterone was determined by radioimmunoassay (Immunotech, Beckman Coulter Company, Marseille, France) and expressed in picomols per liter (pmol/l). Plasma renin activity (ng/ml/h) was measured by quantitative determination of angiotensin I using a commercially available radioimmunoassay kit produced by DiaSorin S.p.A., Saluggia (VC), Italy. The analytical sensitivity of this assay was 0.20 ng/ml, intra-assay CV 5.4% and inter-assay CV 7.5%, respectively. The cross reactivity with angiotensin II, heptapeptide and hexapeptide was below 0.02%. We established our own reference range for PRA in sitting position 0.3-3.5 ng/ml/h. In the cases when PRA was lower than 0.3 ng/ml/h or undetectable it was set at 0.3 ng/ml/h.

2.4. Statistical analysis

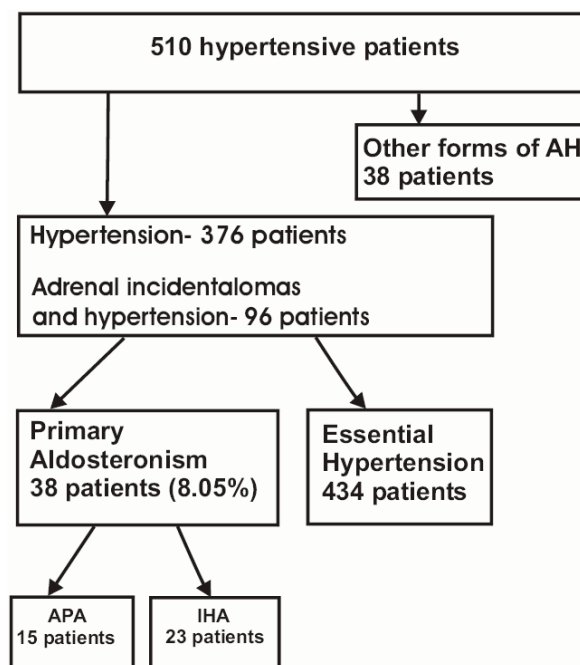
We assessed the prevalence of PA among hypertensive patients, including cases with adrenal incidentalomas, and the prevalence of APA and IHA among cases with PA. We compared age, gender, clinical history, blood

pressure, body mass index, serum potassium, PRA and aldosterone between patients with PA and patients with essential hypertension (EH). Differences in categorical data were tested with Chi-square test and results are expressed as proportion. The Kolmogorov-Smirnov test was used in order to determine the distribution of continuous data. Differences in normally distributed variables were analyzed by Student's *t* test and results are reported as mean $\pm$ SD. Mann-Whitney test was used to analyze data with non-normal distribution and results are expressed as median [interquartile range]. Pre- and postoperative data of patients with PA were analyzed using the Wilcoxon rank-sum test. Significance level was fixed at 0.05 everywhere.

3. Results

510 consecutive hypertensive patients were investigated between October 2005 and October 2008. Other causes of endocrine hypertension except PA were found in 38 patients (these included pheochromocytoma, subclinical hypercortisolism, thyroid dysfunction, renovascular or renal hypertension, or congenital adrenal hyperplasia). Among the remaining 472 patients 376 patients were referred for exploration of hypertension and 96 patients were referred for hypertension associated with adrenal incidentaloma. In the group of hypertensive patients with adrenal incidentaloma 12 patients (12.5%) were found to have PA (aldosterone-producing adenoma). Among the 376 patients referred for hypertension we identified 26 cases (6.9 %) with PA (3 APA and 23 IHA). Consequently, in the entire hypertensive population of 472 patients, final diagnosis of PA was reached in 38 patients, which represents a prevalence of 8.05%, and the remaining patients were diagnosed with EH

Figure 1. Prevalence of primary aldosteronism among hypertensive patients; APA- aldosterone-producing adenoma; IHA- idiopathic hyperaldosteronism; AH- arterial hypertension



(Figure 1). No patients with glucocorticoid-remediable aldosteronism were diagnosed among subjects with PA.

The comparison between patients with PA and essential hypertensive patients is presented in Table 1. There was no significant difference in body mass index or in family history of hypertension between the two groups. Patients with PA were older, more often men, had longer duration of hypertension, higher systolic and diastolic blood pressure, as well as higher percentage of patients on antihypertensive treatment at time of investigation. As expected, patients with PA had lower

Table 1. Comparison of patients with primary aldosteronism (PA) and essential hypertension (EH). Values are expressed as number of patients (percent), mean {plus minus} SD or median [interquartile range], as appropriate.

Variable	PA (n=38)	EH (n=434)	p value
Males, %	19 (50.0)	142 (32.7)	0.031
Family history of hypertension, %	25 (69.4)	268 (69.3)	0.981
Age at presentation, y	54 [44-60]	49 [36-58]	0.028
Duration of hypertension, y	13 [5-20]	5 [2-10]	<0.001
Antihypertensive treatment, %	35 (92.1)	272 (64.5)	0.001
Systolic blood pressure, mmHg	155 [140-170]	140 [130-150]	0.001
Diastolic blood pressure, mmHg	100 [80-100]	90 [80-100]	0.021
Body mass index, kg/m ²	29.1 $\pm$ 5.9	29.1 $\pm$ 6.5	0.989
Serum potassium, mmol/l	4.2 $\pm$ 0.7	4.8 $\pm$ 0.5	<0.001
Serum aldosterone, pmol/l	877 [515-1373]	229 [111-408]	<0.001
Plasma renin activity, ng/ml/h	0.3 [0.3-0.3]	0.54 [0.3-1.33]	<0.001
Aldosterone to renin ratio, pmol/ ng/ml/h	2275 [1594-3749]	348 [163-737]	<0.001

Table 2. Comparison of pre- and postoperative characteristics of patients with aldosterone-producing adenoma. Values are expressed as median [interquartile range].

Variable	Preoperative values	Postoperative values	p
Systolic blood pressure, mmHg	160 [142-160]	130 [115-135]	0.041
Diastolic blood pressure, mmHg	100 [100-112]	80 [80-90]	0.042
K, mmol/l	3.5 [2.8-4.3]	4.8 [4.5-5.1]	0.043
Plasma renin activity, ng/ml/h	0.3 [0.3-0.3]	1.36 [0.70-2.0]	0.043
Serum aldosterone, pmol/l	1085 [533-3106]	199 [65-668]	0.028

potassium levels, higher serum aldosterone, lower PRA and higher ARR than subjects with EH.

In the whole group of patients most of hypertensive subjects presented with mild to moderate hypertension (22.7% of patients had normal or high normal BP (as a result of treatment), 36.9% of patients presented with hypertension grade 1, 25.6% had hypertension grade 2 and 14.8% of patients - hypertension grade 3). The prevalence of PA in the different hypertension groups was as follows: 4.7% among patients with normal and high normal BP, 5.7% among patients with hypertension grade 1, 8.3% among patients with hypertension grade 2, 18.6% among patients with hypertension grade 3. In the group of patients with PA 13.2% had high normal BP, 26.3% were with hypertension grade 1, 26.3% had hypertension grade 2 and 34.2% - hypertension grade 3.

In a group of patients with PA, 17 patients presented with an adrenal nodule on the CT scan or MRI. Postoperatively in two patients the histological result showed adrenal hyperplasia and they were considered to have IHA. Thus, in the PA group 15 patients (39.5%) were diagnosed with APA (12 patients from the hypertensive subgroup with adrenal adenomas and 3 patients in the subgroup of hypertension without adrenal tumors) and 23 patients (60.5%) were found to have IHA. Among all subjects with PA 21 (55.3%) presented with hypokalemia; in the APA group ten patients (66.7%) were hypokalemic whereas in the IHA group 11 patients had hypokalemia (47.8%).

Pre- and postoperative characteristics of patients with APA are shown in Table 2. In all patients hypokalemia was corrected, while hypertension was cured in four patients and was improved in all the remaining patients.

4. Discussion

4.1. Prevalence of PA

We undertook this study to evaluate the prevalence of PA among hypertensive patients in the main Clinical centre of endocrinology in Bulgaria. In contrast to previous studies, which were performed in Hypertension

centers [10,11,13], our patients were investigated in a specialized Clinic of pituitary and adrenal diseases and the prevalence of PA was evaluated not only in the entire hypertensive population, but also among hypertensive patients with adrenal incidentalomas. PA was confirmed in 8.05% of the cases with hypertension in the whole group, in 12.5% among hypertensive patients with adrenal incidentalomas and in 6.9% of hypertensive patients after excluding subjects with proved adrenal adenoma. This corroborated the findings of other investigators that PA is a common form of endocrine hypertension [2,10,11,13-19], therefore we expect that in a larger controlled epidemiological study on the prevalence of PA in Bulgaria this percentage will be confirmed. However it is still an ongoing debate whether all hypertensive patients should be screened for PA or should the testing be performed only in cases with resistant hypertension, adrenal incidentaloma and hypokalemia [3,4]. Recent studies on the prevalence of PA have been criticized for potential selection bias resulting in an overrated number of diagnosed cases and for overestimating the ARR as a diagnostic test for PA leading to unnecessary expensive or unsafe confirmatory tests [3]. On the other hand it has been recognized that patients with PA are at increased cardio-vascular risk [7,8] or risk of renal damage [20]. Both in vitro and clinical studies have described a possible association between PA and carbohydrate metabolism disorders, pointing out aldosterone as a potential contributing factor in the development of the metabolic syndrome and insulin resistance [21-23]. The latter findings give us reason to believe that clinicians should aim at an early diagnosis of PA among hypertensive patients and especially in patients with adrenal incidentalomas and the relatively high prevalence of PA found by our study is a confirmation in this sense.

4.2. Study population

It has been recognized that the prevalence of PA largely depends on the type of the study population and PA is more common in patients with resistant hypertension with a prevalence of about 20% [13,19], than in patients with mild to moderate hypertension where the rate is

about 6% [24]. Since in Bulgaria patients with resistant hypertension are referred to a Cardiology, Nephrology or Endocrinology departments rather than to a specialized Hypertension center, our study population was not homogenous. It consisted mainly of patients with mild to moderate hypertension, as well as a smaller number of patients with resistant hypertension or with paroxysmal hypertension. Our results confirm the findings of other investigators [17], as data showed that PA is most frequently diagnosed in patients with grade 3 hypertension with a prevalence of 18.33%, whereas the prevalence among grade 2 or grade 1 hypertensive subjects is much lower.

4.3. Screening and confirmatory tests

The majority of our patients with APA or IHA were hypokalemic. A likely explanation could be a possible preselection of patients, since some hypertensive patients with a previously diagnosed hypokalemia have been referred and hospitalized in our specialized Clinic of pituitary and adrenal diseases.

Since its description in 1985 [25] the ARR has been widely used in the diagnostic algorithm for PA. Although some reports claim that the ARR could be measured without discontinuing the antihypertensive medication [26], most studies have shown that beta-blockers, ACE-inhibitors and diuretics could substantially affect renin and aldosterone measurements [27], consequently these drugs were stopped before the investigation of our patients. Although the use of confirmatory testing for the diagnosis of PA is a controversial issue [28], the simple measurement of the ARR has a relatively poor positive predictive value [29]. The Captopril test was used for confirmation of PA, because in addition to the fact that it could be easily and safely performed, several reports proved its effectiveness in the diagnosis of PA [11,30]. Though the latter has been challenged by some investigators [31], a recent study by Rossi et al. used a head-to-head comparison of the Captopril and the saline infusion test, showing that the two tests are equally

effective for diagnosing APA [32]. Therefore we used the Captopril test as a confirmatory test in our diagnostic algorithm for PA.

As it concerns the differential diagnosis of PA, AVS is regarded as the best method for discriminating APA from IHA [33-35]. Although according to most classifications of PA IHA accounts for about 60% of cases and APA for about 35% [36], recently it was shown that in centers using AVS, APA was diagnosed more often than IHA [2,16,20]. Therefore the proportions of IHA and APA in our study might have been different if AVS had been used in the diagnostic algorithm and it is possible that some cases with IHA were misdiagnosed as APA on the basis of the identification of an apparent nodule on CT/MRI. Also, it is possible that the reverse occurred, and the high prevalence of hypokalemia could be partly explained by an underestimation of the number of patients with APA, because they tend to have lower potassium levels than patients with IHA [37].

In conclusion, this is the first study designed to assess the prevalence of PA in hypertensive patients referred to a specialized Clinic of pituitary and adrenal diseases in the principal Centre of Endocrinology in Bulgaria. This study was not an epidemiological one, which precluded selection bias, but it focused the attention on the high prevalence of PA in hypertensive subjects. Since PA is a potentially curable form of hypertension (surgically for APA and medically for IHA) our findings support an early screening and diagnosis of PA, and especially in hypertensive patients with adrenal incidentalomas.

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