Thieme

Prevalence of Primary Aldosteronism in Newly Diagnosed Hypertensive Patients in Primary Care

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ABSTRACT

Context Primary aldosteronism (PA) represents the most frequent cause of endocrine arterial hypertension. PA is also common in patients with mild forms of hypertension and normokalemia.

Objective To identify the prevalence of PA in newly diagnosed hypertensive patients in primary care in Southern Germany.

Patients and methods Newly diagnosed hypertensive patients in 27 primary care centers in Munich agreed to participate in the study. Patients were screened for PA using the aldosterone-to-renin ratio (ARR). In case of elevated ARR, confirmation testing was performed. After the diagnosis of PA, subtype differentiation and subsequent therapy of PA were initiated.

Results A total of 235 patients with newly discovered arterial hypertension were initially screened for PA. Among these, 35 were excluded because the medication indicated pre-existing treated arterial hypertension or they were on interfering antihypertensive medication. At the first screening, 2.0 % of the patients had hypokalemia. Of the 200 patients with newly discovered arterial hypertension, 42 had an elevated ARR. The incidence of the presence of hypokalemia did not differ according to normal or pathological ARR. Nine patients (21 %) did not show up for further testing and were lost to follow-up, and 33 patients underwent a saline infusion test. Of these, 11 patients were diagnosed with PA, leading to at least 5.5 % prevalence of PA in the collective. None of the diagnosed PA patients was hypokalemic at screening.

Conclusion A 5.5 % prevalence of PA was observed in our data of untreated newly diagnosed patients with hypertension.

Introduction

Primary aldosteronism (PA) is hypertension caused by inappropriately high aldosterone secretion, consecutively low plasma renin, and elevated aldosterone-to-renin ratio (ARR). It represents the most frequent cause of endocrine arterial hypertension and is found in 5.8 % of unselected hypertensive patients in primary care, 6–12 % in hypertension centers, and up to 30 % in patients with resistant hypertension [1]. Although the disease was previously considered to be present only in patients with severe hypertension and hypokalemia, it is now well known that PA is also common in patients with mild forms of hypertension and normokalemia.

As patients with PA suffer from an increased risk of cardio- and cerebrovascular events and metabolic abnormalities, early identification and therapy of the affected patients are of great importance [2]. Most of the patients are affected by sporadic forms: unilateral aldosteronism, mainly caused by aldosterone-producing adenoma (APA), which can be cured by adrenalectomy; and bilateral hyperaldosteronism, mostly caused by idiopathic adrenal hyperplasia (IAH), which can be managed by life-long administration of mineralocorticoid receptor (MR) antagonists [3]. A recent meta-analysis found a good long-term prognosis after specific therapy; at years 5 and 7, the mortality decreased progressively below the level of essential hypertension (EH). This effect was even more pro-

nounced in patients with APA following unilateral adrenalectomy [4]. In this line, Hundemer et al. demonstrated that medically treated PA patients had a higher cardiovascular risk compared to adrenalectomized patients, despite similar blood pressure (BP) levels [5]. Yet, those patients with medically induced renin stimulation had a similar risk compared to those who were operated upon. Medically treated PA patients have a higher risk of atrial fibrillation compared to those with EH, whereas adrenalectomized patients do not display an increased risk [6].

With the widespread introduction of the sensitive screening method using ARR, awareness has increased in primary care [7]. Nevertheless, PA still remains an underdiagnosed and undertreated disease because screening is not universally followed [8].

We aimed to identify the prevalence of PA in newly diagnosed hypertensive patients in primary care in Southern Germany.

Patients and Methods

Study population

A total of 27 primary care centers in Munich agreed to participate in the study. The study was performed from 2012–2016. The primary care centers were part of a medical school teaching network at LMU for general medicine. We sent out a call to the 100 primary care centers of this network to participate, and 27 responded. In these centers, subjects with routine appointments and no known diagnosis of arterial hypertension were checked for elevated BP. If positive, our study team was contacted, and the patient was seen again in the primary care center for informed consent, blood pressure (BP) control, and blood withdrawal. The diagnosis of hypertension was obtained by three consecutive office BP measurements in the sitting position on each arm using a mercury sphygmomanometer, according to European Society of Hypertension guidelines [9]. The classification of BP for adults was according to the Joint National Committee VI, which has established three different stages: stage 1, systolic BP (SBP) 140 to 159, diastolic BP (DBP) 90 to 99; stage 2, SBP 160 to 179, DBP 100 to 109; and stage 3, SBP ≥ 180, DBP ≥ 110 mm Hg. When the systolic and diastolic BP of the patient were in different categories, the higher category was selected to classify the BP status of the individual. When a patient had newly diagnosed arterial hypertension, ARR, sodium, potassium, and creatinine was determined and analyzed in the endocrine laboratory of the Medical Department 4 of the Ludwig-Maximilians-University, Munich. Hypokalemia was defined as serum potassium < 3.5 mmol/l. Diagnosis of PA was made according to the criteria outlined in the guidelines of the Endocrine Society as described before [10–12]. In short, PA patients had an elevated ARR (> 12 ng/mU) with an elevated aldosterone (> 5 ng/dL) and an abnormal confirmatory test (saline infusion test in the seated position or captopril test). Criteria for abnormal saline infusion testing was a plasma aldosterone > 5 ng/dL at 240 minutes, and for abnormal captopril testing, a drop in plasma aldosterone of < 30 % in the presence of a continuously suppressed plasma renin concentration. Subtypes were differentiated by adrenal imaging followed by adrenal vein sampling (AVS) without adrenocorticotropic hormone stimulation, as described earlier [13, 14]. We used a selectivity index of ≥ 2 and a lateralization index of ≥ 4 for the diagnosis of unilateral aldosterone excess.

Analytical methods

Blood samples were drawn in a fasting state in a sitting position. Plasma aldosterone measurements were performed with the radioimmunoassay "aldosterone Coat-a-Count" (Biermann DPC). Direct renin concentration was measured by the Liaison chemiluminescence assay (Diasorin). In our hands, the respective within- and between-assay coefficients of variation were less than 9 and 12 % for aldosterone and less than 5.6 and 12.2 % for renin. All other analyses were performed in our central laboratory using standard methods.

Statistics and Ethics

A sample size of 200 was calculated to estimate the prevalence of hyperaldosteronism with a two-sided 95 % confidence interval of maximal width of 10 % (+/−5 %). If not stated otherwise, results were expressed as median and 25^{th} – 75^{th} percentiles. Data between groups were compared using the Mann-Whitney U test. Within group changes from baseline to follow-up were calculated by the Wilcoxon signed-rank-test. $\chi 2$ test was used to compare frequency distributions. $P < 0.05$ was considered to be statistically significant. Statistical analysis was performed using standard statistical software (SPSS 27, IBM USA). The study and the German Conn's registry have been approved by the local ethical committee (358–12). All subjects agreed to participate in the study.

Results

Characteristics of the study population at diagnosis

Two-hundred thirty-five patients with newly discovered arterial hypertension were initially screened for PA. Of these patients, 35 were excluded because the chronic medication indicated pre-existing treated arterial hypertension or they were on interfering antihypertensive medication. The final cohort consisted of 200 patients. Four (2.0 %) of the patients had hypokalemia at the first screening. The characteristics of these 200 patients are described in ▶ **Table 1**. One-hundred and seven (53.5 %) of the patients had hypertension stage 1, 68 (34.0 %) had hypertension stage 2, and 25 (12.5 %) had hypertension stage 3.

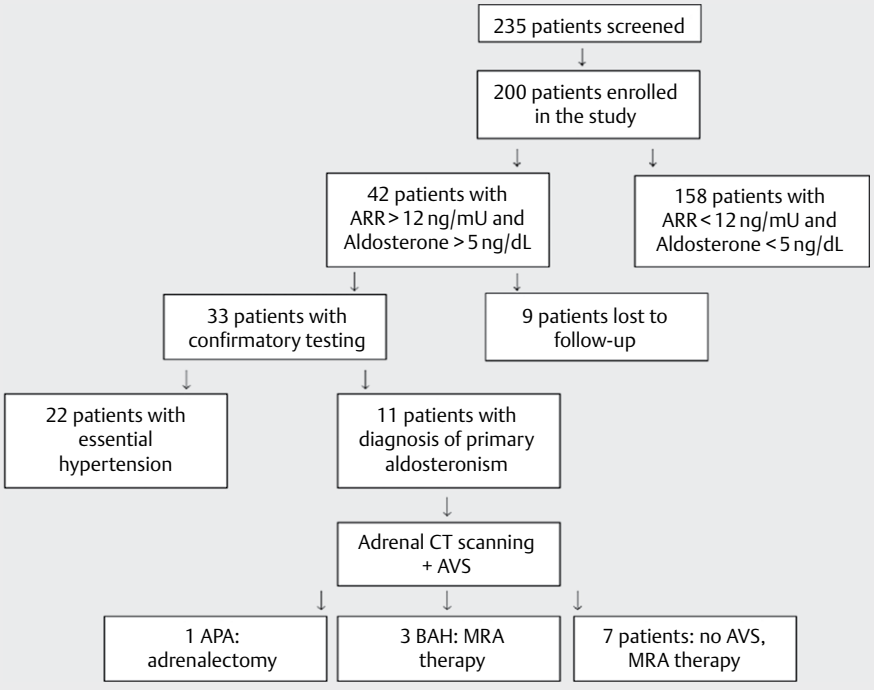
Incidence of elevated aldosterone to renin ratio in the study population

Of the 200 patients with newly discovered arterial hypertension, 42 (21 %) had an elevated ARR (> 12 ng/mU) and a plasma aldosterone concentration > 5 ng/dL (▶ **Fig. 1**). Patients with pathological ARR were older (48.0 (39.5; 58.0) years) than patients with normal ARR (40.0 (31.0; 53.0) years) ($p = 0.07$). The incidence of the presence of hypokalemia did not differ according to normal or pathological ARR ($p = 0.298$). The prevalence of an elevated ARR was higher in stage 2 hypertension (27.9 %) than in stage 1 (19.6 %), but was low in stage 3 (8 %, $p = 0.098$, ▶ **Fig. 2**).

▶ **Table 1** Characteristics of the 200 patients included in the study and comparison of patients with PA and EH. Nine patients had positive ARR but did not undergo confirmatory testing for PA and were lost to follow-up.

	Patients (n = 200)	PA (n = 11)	EH (n = 180)	p
Age (years)	42 (32; 53)	46 (41; 60)	42 (31; 53)	0.126
Sex (male/female)	127/73	7/4	118/62	0.897
SBP (mmHg)	149 (140; 158)	156 (140; 160)	149 (140; 157)	0.369
DBP (mmHg)	95 (90; 100)	94 (90; 100)	94 (90; 100)	0.793
BMI (kg/m2)	26.0 (24.1; 29.9)	26.2 (24.5; 33.3)	26.3 (24.2; 30.1)	0.734
Serum aldosterone (ng/dL)	8.8 (5.5; 13.7)	11.2 (8.3; 15.9)	8.5 (5.1; 13.3)	**0.027**
Renin mU/L	14.2 (8.6; 24.4)	4.4 (2.0; 6.5)	15.8 (9.7; 25.5)	**0.001**
ARR (ng/mU)	5.8 (3.7; 10.7)	39.0 (14.5; 64.1)	5.4 (3.6; 9.5)	**0.001**
Serum potassium (mmol/L)	4.0 (3.8; 4.2)	3.9 (3.6; 4.4)	4.0 (3.8; 4.2)	0.468
Hypokalemic at screening	4	0	4	0.617
Serum creatinine (mg/dL)	0.9 (0.7; 1.0)	0.9 (0.7; 1.1)	0.9 (0.7; 1.0)	0.417

Data are given as median (25th to 75th percentile).; Abbreviations: EH, essential hypertension; PA, primary aldosteronism; SBP, systolic blood pressure; DBP, diastolic blood pressure; ARR, aldosterone-to-renin ratio.

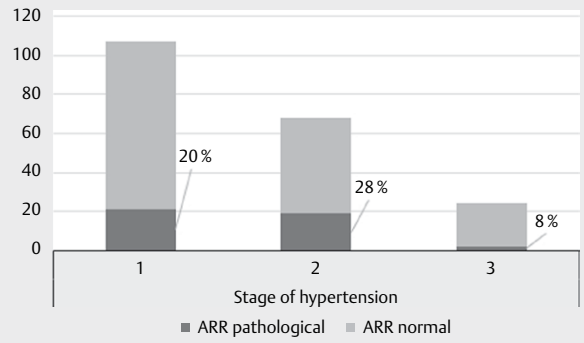


▶ **Fig. 1** Study Flow chart.

Incidence of primary aldosteronism in the study population

All 42 patients with elevated ARR were contacted to perform confirmatory testing. Nine patients (21.4 %) did not show up for further testing and were lost to follow-up, and 33 of 42 patients underwent a saline infusion test (seven patients had an additional captopril test when the results were inconclusive). Of these, 11 patients were diagnosed with PA (▶ **Fig. 1**), leading to a prevalence of at least 5.5 % of PA in the collective. None of the diagnosed PA patients was hypokalemic at screening. A study by Kanaan et al. showed that a potassium concentration of 3.8 mmol/L or lower (" < 3.9 mmol/L") best-discriminated patients with PA from with EH when only this information is available [15]. In our study, 5 (45.5 %) of patients with PA had a serum-K below 3.9 mmol/L compared to 48 (26.7 %) (p = 0.179) of the non-PA subjects. The patients with EH and those with PA did not differ in their BP levels (see ▶ **Table 1**). Five of the patients with PA had hypertension stage 1, five had stage 2, and one patient had stage 3.

According to current guideline recommendations, AVS and CT were proposed to the 11 newly diagnosed PA patients. A minority



▶ **Fig. 2** Prevalence of pathological ARR depending on Hypertension Stage.

of four patients chose to perform further subtyping. One of these patients was diagnosed with unilateral PA and treated by unilateral adrenalectomy. Three patients were diagnosed with bilateral PA, and treatment with MR-antagonist was started. In the remaining seven patients without AVS, MRA therapy was recommended; five of these patients were lost to follow-up.

Discussion

In one retrospective study of patients with resistant hypertension in California (n = 4660), the screening rate for PA was 2.1 % [16]. Similarly, a retrospective study of veterans in the USA with treatment-resistant hypertension (n = 269 010) showed that 1.6 % of the participants had PA. A visit to a nephrologist or an endocrinologist was associated with a higher likelihood of testing compared with primary care [17]. Testing was associated with a 4-fold higher likelihood of MRA treatment and better BP control. This underlines the importance of implementing guideline-recommended practices in managing patients with treatment-resistant hypertension. Yet, currently, many PA patients are not diagnosed due to missing screening procedures. The 2016 Endocrine Society guideline recommends screening for PA in all hypertensive patients with a high risk of PA, which applies to more than half of the hypertensive population [3]. According to a recent survey, renin and aldosterone measurements are only performed in 7 % of general practitioners in Italy and 8 % in Germany, with accordingly low PA prevalence of 1 % and 2 %, respectively [8]. Along the same line, measurement of potassium levels at diagnosis of hypertension occurred in only 43 % of the general practitioners in Italy and 58 % in Germany.

Previous data estimated a 2.6–12.7 % prevalence of PA in unselected hypertensives [1, 18, 19] and up to 20 % in patients with resistant hypertension [20]. Our data on untreated, newly diagnosed patients with hypertension perfectly align with these data; based on confirmatory testing, 5.5 % of the total cohort had PA. When analyzing the prevalence of PA according to hypertension grade, the literature reports a prevalence of 2.0–6.6 in grade I, 8.0–15.5 in grade II, and 11.8–19 % in grade III hypertension [1, 18, 19, 21]. In our study, the rate of pathological ARR did not differ according to the hypertension stage. This could be caused by the low number of patients.

In the Primary Aldosteronism in Torino (PATO) study, unselected hypertensive patients (n = 1672) in primary care were prospectively screened. They reported a prevalence of 5.9 % of patients with a diagnosis of PA [18], similar to 5.5 % in our study. PA prevalence increased with the severity of hypertension, but 44 % of the identified cases were affected by stage I hypertension, very close to 45.5 % in our study. A meta-analysis comprising 36, 614 patients from hypertension units and 5896 patients from primary care reported a prevalence of PA in hypertension units in the range of 0.7 – 29.8 % and 3.2–12.7 % in primary care [22]. Our data showed a prevalence of 5.5 % of PA in this cohort of newly diagnosed hypertensive patients in primary care.

In the PATO study cohort, 65 % of patients were diagnosed with bilateral disease compared with 27 % with unilateral PA; 8 % had an undetermined subtype because either these patients refused AVS or the AVS results were inconclusive. In our study, 27 % of the patients were diagnosed with bilateral disease, and only 9 % with APA; 64 % did not perform AVS and directly started therapy with MRA without further subtyping or were lost to follow-up.

Hypokalemia is observed in only 25–40 % of PA patients [18, 23]. In our study, none of the patients with PA was hypokalemic, while 2.2 % had EH.

Our goal was to analyze the incidence of PA in newly diagnosed, untreated hypertensive patients in primary care. In conclusion, our data of untreated newly diagnosed patients with hypertension confirm a prevalence of 5.5 % of PA, quite similar to other studies on treated patients with hypertension in primary care. The data can be used to address health care providers and to advance the care of hypertensive patients who are affected by an endocrine disease. The early identification of PA patients is crucial due to the high burden of cardiovascular comorbidities that these patients display at the time of diagnosis, which are reversible through adequate therapy.

Limitations of the study

The total number of total patients was low. Nine of 42 patients with elevated ARR were lost to follow-up and could not be further evaluated, possibly leading to a slightly lower prevalence of PA. Five of the 11 patients with PA were lost to follow up, leading to a low fraction of subtyping. The collection of outcome data was not a part of the protocol (cardiovascular outcome data).

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Conflict of Interest

The authors have no conflict of interest to declare

References

[1] Yang Y, Reincke M, Williams TA. Prevalence, diagnosis and outcomes of treatment for primary aldosteronism. Best Pract Res Clin Endocrinol Metab 2020; 34: 101365. doi:10.1016/j.beem.2019.101365

[2] Monticone S, D'Ascenzo F, Moretti C et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: A systematic review and meta-analysis. Lancet Diabetes Endocrinol 2018; 6: 41–50. doi:10.1016/S2213-8587(17)30319-4

[3] Funder JW, Carey RM, Mantero F et al. The management of primary aldosteronism: Case detection, diagnosis, and treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2016; 101: 1889–1916. doi:10.1210/jc.2015-4061

[4] Meng Z, Dai Z, Huang K et al. Long-term mortality for patients of primary aldosteronism compared with essential hypertension: A systematic review and meta-analysis. Front Endocrinol (Lausanne) 2020; 11: 121. doi:10.3389/fendo.2020.00121

[5] Hundemer GL, Curhan GC, Yozamp N et al. Cardiometabolic outcomes and mortality in medically treated primary aldosteronism: A retrospective cohort study. Lancet Diabetes Endocrinol 2018; 6: 51–59. doi:10.1016/S2213-8587(17)30367-4

[6] Rossi GP, Maiolino G, Flego A et al. Adrenalectomy lowers incident atrial fibrillation in primary aldosteronism patients at long term. Hypertension 2018; 71: 585–591. doi:10.1161/HYPERTENSIONAHA.117.10596

[7] Buffolo F, Monticone S, Tetti M et al. Primary aldosteronism in the primary care setting. Curr Opin Endocrinol Diabetes Obes 2018; 25: 155–159. doi:10.1097/MED.0000000000000408

[8] Mulatero P, Monticone S, Burrello J et al. Guidelines for primary aldosteronism: Uptake by primary care physicians in Europe. J Hypertens 2016; 34: 2253–2257. doi:10.1097/HJH.0000000000001088

[9] Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013; 34: 2159–2219. doi:10.1093/eurheartj/eht151

[10] Funder JW, Carey RM, Fardella C et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2008; 93: 3266–3281

[11] Fischer E, Adolf C, Pallauf A et al. Aldosterone excess impairs first phase insulin secretion in primary aldosteronism. J Clin Endocrinol Metab 2013; 98: 2513–2520. doi:10.1210/jc.2012-3934

[12] Fischer E, Hanslik G, Pallauf A et al. Prolonged zona glomerulosa insufficiency causing hyperkalemia in primary aldosteronism after adrenalectomy. J Clin Endocrinol Metab 2012; 97: 3965–3973. doi:10.1210/jc.2012-2234

[13] Betz MJ, Degenhart C, Fischer E et al. Adrenal vein sampling using rapid cortisol assays in primary aldosteronism is useful in centers with low success rates. Eur J Endocrinol 2011; 165: 301–306. doi:10.1530/EJE-11-0287

[14] Vonend O, Ockenfels N, Gao X et al. Adrenal venous sampling: Evaluation of the German Conn's registry. Hypertension 2011; 57: 990–995. doi:10.1161/HYPERTENSIONAHA.110.168484

[15] Kanaan E, Haase M, Vonend O et al. Aldosterone-mediated sodium retention is reflected by the Serum Sodium to Urinary Sodium to (Serum Potassium)(2) to Urinary Potassium (SUSPPUP) index. Diagnostics (Basel) 2020; 10. doi:10.3390/diagnostics10080545

[16] Jaffe G, Gray Z, Krishnan G et al. Screening rates for primary aldosteronism in resistant hypertension: A cohort study. Hypertension 2020; 75: 650–659. doi:10.1161/HYPERTENSIONAHA.119.14359

[17] Cohen JB, Cohen DL, Herman DS et al. Testing for primary aldosteronism and mineralocorticoid receptor antagonist use among U.S. veterans: A retrospective cohort study. Ann Intern Med 2020. doi:10.7326/M20-4873. doi:10.7326/M20-4873

[18] Monticone S, Burrello J, Tizzani D et al. Prevalence and clinical manifestations of primary aldosteronism encountered in primary care practice. J Am Coll Cardiol 2017; 69: 1811–1820. doi:10.1016/j.jacc.2017.01.052

[19] Mosso L, Carvajal C, Gonzalez A et al. Primary aldosteronism and hypertensive disease. Hypertension 2003; 42: 161–165. doi:10.1161/01.HYP.0000079505.25750.11

[20] Calhoun DA, Nishizaka MK, Zaman MA et al. Hyperaldosteronism among black and white subjects with resistant hypertension. Hypertension 2002; 40: 892–896. doi:10.1161/01.hyp.0000040261.30455.b6

[21] Rossi GP, Bernini G, Caliumi C et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. J Am Coll Cardiol 2006; 48: 2293–2300. doi:10.1016/j.jacc.2006.07.059

[22] Kayser SC, Dekkers T, Groenewoud HJ et al. Study heterogeneity and estimation of prevalence of primary aldosteronism: A systematic review and meta-regression analysis. J Clin Endocrinol Metab 2016; 101: 2826–2835. doi:10.1210/jc.2016-1472

[23] Buffolo F, Monticone S, Burrello J et al. Is primary aldosteronism still largely unrecognized? Horm Metab Res 2017; 49: 908–914. doi:10.1055/s-0043-119755