Primary aldosteronism: key characteristics at diagnosis: a trend toward milder forms

Daniel A Heinrich¹, Christian Adolf¹, Lars C Rump², Ivo Quack², Marcus Quinkler³, Stefanie Hahner⁴, Andrzej Januszewicz⁵, Jochen Seufert⁶, Holger S Willenberg⁷, Nina Nirschl¹, Lisa Sturm¹, Felix Beuschlein^{1,8} and Martin Reincke¹

¹Medizinische Klinik und Poliklinik IV, Klinikum der Universität, LMU München, München, Germany, ²Department of Nephrology, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany, ³Endocrinology in Charlottenburg, Berlin, Germany, ⁴Medizinische Klinik und Poliklinik I, Schwerpunkt Endokrinologie und Diabetologie, Universitätsklinikum Würzburg, Würzburg, Germany, ⁵Department of Hypertension, Institute for Cardiology, Warsaw, Poland, ⁶Division of Endocrinology and Diabetology, Faculty of Medicine, University of Freiburg Medical Center, University of Freiburg, Freiburg, Germany, ⁷Division of Endocrinology and Metabolism, Rostock University Medical Center, Rostock, Germany, and ⁸Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, Universitäts-Spital Zürich, Zürich, Switzerland

Correspondence should be addressed to M Reincke
Email
martin.reincke@med.uni-muenchen.de

Abstract

Objective: Primary aldosteronism (PA) is the most common endocrine form of arterial hypertension. The German Conn's Registry's purpose is to improve treatment outcomes of PA. We assessed whether key clinical, biochemical and epidemiological characteristics of newly diagnosed PA cases have changed over time, potentially indicating a different screening and referral practice in Germany evolving from 2008 to 2016.

Design: The German Conn's Registry is a multicenter database prospectively analyzing morbidity and long-term outcome of patients with PA.

Methods: Phenotypic changes between three year periods were calculated using Mann–Whitney *U* tests and Kruskal–Wallis tests for independent variables.

Results: Over three time periods from 2008 to 2016, we noted a relative decrease of unilateral PA cases (67 vs 43%). Significantly more females were diagnosed with PA (33 vs 43%). Median daily defined drug doses decreased (3.1 vs 2.0) in the presence of unchanged SBP (150 vs 150 mmHg), plasma aldosterone (199 vs 173 ng/L) and PRC (3.2 vs 3.2 U/L). Median ARR values decreased (70 vs 47 ng/U) and median potassium levels at diagnosis (3.5 vs 3.7 mmol/L) increased as the percentage of normokalemic patients (25 vs 41%), indicating milder forms of PA.

Conclusions: Our results are in accordance with an increased screening intensity for PA. We identified a trend toward diagnosing milder forms, increasingly more females and less unilateral cases of PA.

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Introduction

Primary aldosteronism (PA) is the most common endocrine form of arterial hypertension. Prevalence estimates range from 5 to 13% among different studies and cohorts (1, 2, 3, 4, 5). Originally described by Jerome Conn in 1955, the classic PA triad comprises hypertension, hypokalemia and metabolic alkalosis (6). Common causes of PA include bilateral adrenal hyperplasia (BAH) or unilateral aldosterone-producing adenoma (APA).

Patients diagnosed with a bilateral disease may be treated with a mineralocorticoid receptor antagonist (MRA). APA patients can be surgically cured by unilateral adrenalectomy (uADX) (5).

Considered as a cardiovascular risk factor, long-term elevated aldosterone levels lead to end-organ damage, including cardiac and renal impairment (7, 8, 9). PA patients have higher rates

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of myocardial infarction, stroke and atrial fibrillation compared to matched hypertensives (10, 11, 12, 13, 14). Nevertheless, even though all information is accessible, PA remains highly unknown and underdiagnosed among physicians (15, 16).

One of the purposes of the German Conn's Registry is to improve screening, diagnosis and subtyping of this disease, which often seems to be viewed as an orphan disorder. In accordance, there have been even calls for a systematic screening of all hypertensive patients (17). This would include stage I hypertensive patients who are not screened according to current guidelines (5). A more favorable outcome for early diagnosis and treatment has been recently shown in the PASO study, especially for younger female PA patients (18).

The German Conn's Registry was founded in 2008. Herein, we made use of the data set to assess, whether key clinical, biochemical and epidemiological characteristics of newly diagnosed PA cases have changed over time, indicating a different screening and referral practice in German Conn's Registry centers evolving from 2008 to 2016.

Subjects and methods

Description of the registry and patient cohort

The German Conn's Registry is a multicentric database analyzing morbidity and long-term outcome of patients with PA. Since 2008, all newly diagnosed patients are entered in six centers. Enrolled patients were studied prospectively within the registry. For this analysis, the patients of German centers (Berlin $n=57$, Düsseldorf $n=156$, Freiburg $n=4$, Munich $n=425$, Würzburg $n=38$) and the Polish center (Warsaw: 30, since 2012) treated between 01.01.2008 and 31.12.2016 were included. All patients gave written informed consent. The German Conn's Registry participants use the same standard operational procedures for office blood pressure measurements, adjustment of medication during aldosterone-to-renin ratio (ARR) determination and confirmatory testing, confirmatory testing by saline infusion test and adrenal vein sampling (AVS; without ACTH stimulation). The ethics committees of the University of Munich and of the participating centers approved the protocol. Data protection laws were strictly adhered to. At the time of diagnosis, patients underwent standard procedures including collection of anthropometric data and laboratory testing.

Diagnostic work-up

The diagnostic work-up was performed in accordance with the Endocrine Society Practice Guidelines (5, 19). PA diagnosis was established by an elevated plasma ARR (cut-off 10.0 ng/U, sitting position) and an abnormal confirmatory test (e.g. salt loading test, captopril challenge test or both, fludrocortisone suppression test). The centers used the following assays for aldosterone and plasma renin concentration (PRC) measurements: Berlin: aldosterone: Siemens Coat-a-Count RIA or Diasorin Liaison CLIA, PRC: Diasorin Liaison, Diasorin Liaison Act or IRMA Schering Berlin; Düsseldorf: aldosterone: Siemens Coat-a-Count RIA, PRC: Diasorin Liaison Act.; Freiburg: aldosterone: DiaSorin Liaison CLIA, PRC: Diasorin Liaison Direct renin; Munich: aldosterone: 2008–2013: Siemens Coat-a-Count RIA, 2014–2016: DiaSorin Liaison CLIA, PRC: Diasorin Liaison Act.; Würzburg: aldosterone: Siemens Coat-a-Count RIA, PRC: IRMA Schering Berlin; Warsaw: aldosterone: Aldo. RIA immunotech/demeditec or RIA DiaSorin Diag., PRC: Renin RIA Schering/Cis-bio). Prior to testing antihypertensive medication was stopped at least for one week (beta blockers, angiotensin-converting-enzyme inhibitors, angiotensin-II-receptor blockers, calcium antagonists, low dose thiazides, renin inhibitors) and 4 weeks (mineralocorticoid antagonists, loop diuretics) whenever possible. Severely hypertensive patients received drugs with minimal effect on the ARR, such as an alpha receptor blocker (doxazosin) or slow release calcium antagonists (verapamil). For subtype differentiation between unilateral and bilateral disease, AVS was performed (20, 21). Patients who were not suitable candidates for surgery or refused surgery did not undergo AVS (noAVS group).

Statistical analysis

All values are expressed as median and 25th and 75th percentile if not mentioned otherwise. To assess changes between three-year periods we used the Chi² trend test for categorical variables and the Jonckheere-Terpstra trend test for quantitative variables. We performed subgroup analysis for gender distribution. The sex-adjusted comparison of the trends for quantitative variables was performed using linear regression calculation and for categorical variables logistic regression calculation. Two-tailed probability values of <5% were considered to be statistically significant. Statistical analysis was performed using standard statistical software (SPSS 24, IBM).

Figures and tables were generated using SPSS 24 or Microsoft Excel 2014.

Results

Since 2008, we have prospectively enrolled 710 PA patients in five German and one Polish center.

Characteristics of patients according to sex and subtype differentiation

In total, 60% ($n=429$) were male and 40% ($n=281$) were female patients. According to AVS, 358 patients were classified to have unilateral disease (139 females and 219 males, $P=0.85$), whereas 230 were identified as bilateral (91 females, 139 males). 122 patients did not undergo AVS (noAVS, 57 females, 65 males). A comparison between males and females is listed in [Supplementary Table 1](#) (see section on [supplementary data](#) given at the end of this article).

Interestingly, the analysis of sex-specific characteristics indicated that males were older than females at PA diagnosis (APA: 54 vs 49 years, $P<0.0005$; BAH: 51 vs 49 years, $P=0.022$). Males received higher defined daily drug doses (DDD) (APA: 3 vs 2.5, $P<0.0005$; BAH: 3 vs 2, $P<0.0005$), had higher systolic blood pressure (SBP) (APA: 156 vs 145 mmHg, $P<0.0005$, APA: 153 vs 145, $P=0.018$) and a longer hypertension history (APA: 6 vs 10 years to PA diagnosis, $P=0.012$, BAH: 10 vs 5, $P=0.025$, noAVS: 13 vs 6, $P=0.007$). Males had an adverse cardiometabolic risk profile including higher body mass index (BMI) (APA: 29 vs 25.4 $P<0.0005$, BAH: 29 vs 26.3, $P=0.006$), higher fasting glucose and HbA1c levels and were more frequently diagnosed with type 2 diabetes mellitus (T2DM) (19.6 vs 7.9%) and coronary artery disease (CAD) (7.3 vs 2.2%).

Patients with APA had higher plasma aldosterone levels than their respective counterparts with BAH (males: 222 vs 173 ng/L, $P=0.001$, females: 242 vs 148 ng/L, $P=0.001$). Similarly, these patients had significantly higher ARR values (males: 77 vs 49 ng/U, $P=0.004$, females: 81 vs 42 ng/U, $P=0.001$) and lower potassium values (males: 3.5 vs 3.7 mmol/L, $P=0.002$, females: 3.5 vs 3.8 mmol/L, $P<0.0005$).

Characteristics of patients: comparison over three time periods: 2008–10; 2011–13; 2014–16

All values over time are listed in [Table 1](#). We grouped the patients into three time periods (2008–2010 (I); 2011–2013

(II); 2014–2016 (III)) according to the date of diagnosis. Over time, the number of newly enrolled patients increased ([Fig. 1](#) and [Table 1](#)). In parallel, we noted a relative decrease of unilateral ($P<0.0005$) PA cases among all enrolled patients ([Fig. 1](#)). The sex distribution changed significantly with more females being diagnosed in recent years ($P<0.0005$). Median DDDs were significantly higher in time period I and II compared to time period III ($P<0.0005$) in the presence of unchanged SBP ($P=0.357$) or DBP ($P=0.244$). Plasma aldosterone values decreased and plasma renin concentration (PRC) increased significantly according to trend tests ($P=0.014$, $P=0.018$), while univariate regression analysis identified a non-significant trend for both values (aldosterone: $P=0.06$, regression coefficient -0.028 ; PRC: $P=0.192$, regression coefficient 0.028). When adjusted for gender distribution, these values did not change (aldosterone: $P=0.075$, regression coefficient -0.027 ; PRC: $P=0.169$, regression coefficient 0.03) and the interaction term remained non-significant (aldosterone: $P=0.679$, PRC: $P=0.169$) indicating that these results cannot be explained by gender. However, median ARR values decreased significantly ($P=0.002$, [Fig. 2](#), upper panel). Median potassium levels at diagnosis increased as the ratio of hypokalemic-to-normokalemic patients (both: $P<0.0005$, [Fig. 2](#), lower panel).

Discussion

Widely acknowledged as the single most important contributor to the worldwide burden of mortality, the treatment of arterial hypertension is considered a main task of every general physician ([22](#)). Nevertheless, optimal blood pressure control remains an unmet goal, in part due to the underdiagnosis of secondary causes including PA ([4](#), [23](#)). Therefore, the identification of PA patients and the subsequent specific treatment are imperative.

From 2008 until 2016, the German Conn's Registry prospectively enrolled 710 patients in six centers. Sex-specific analysis among the subtype cohorts underlined the general finding that men have a higher burden of diseases, as DDDs are higher, and in unilateral PA IFG, increased HbA1c or T2DM are more frequent. In contrast, females with BAH have higher potassium levels, showing a trend toward biochemically less severe disease or modulation of plasma aldosterone levels by female sex steroids.

Remarkably, our patient cohort had less cardiovascular events at diagnosis (CAD: 5.6%, stroke: 1.8% and myocardial infarction: 1.7%) than a recent

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Table 1 Comparison of patient characteristics over time from 2008 to 2016. Data are presented as *n* (%) or as median (25th; 75th percentile). Baseline characteristics of patients are compared over the time periods 2008–10 (I), 2011–13 (II) and 2014–16 (III).

	Total	2008–10 (I)	2011–13 (II)	2014–16 (III)	Significance (trend)	Significance (sex adjusted)
Unilateral PA	358 (50.4)	75 (67)	134 (53.6)	149 (42.8)	<0.0005	<0.0005
Sex (females)	281 (40)	37 (33)	94 (38)	150 (43)	0.04	–
CAD	40 (5.6)	15 (13.4)	8 (3.2)	17 (4.9)	0.012	0.025
MI	12 (1.7)	2 (1.8)	1 (0.4)	9 (2.6)	0.232	0.213
Stroke	13 (1.8%)	4 (3.6)	5 (2)	4 (1.1)	0.099	0.994
Diabetes	117 (16.5)	17 (16)	39 (15.6)	61 (17.5)	0.414	0.349
IFG	79 (11.1)	11 (9.8)	27 (10.8)	41 (11.8)	0.414	0.433
Hypokalemia	478 (68.6)	84 (75)	187 (74.8)	207 (59.5)	<0.0005	<0.0005
Age at AH diagnosis (year)	40 (33; 47)	38 (33; 46)	40 (33; 46)	41 (33; 48)	0.133	0.254
Age at PA diagnosis (year)	51 (43; 59)	50 (42; 59)	51 (43; 60)	51 (44; 59)	0.33	0.223
DDD at diagnosis	2.7 (1.3; 4.5)	3.1 (1.6; 5)	3 (2; 4.8)	2 (1; 4)	<0.0005	<0.0005
BMI (kg/m ²)	27.8 (24.8; 31.4)	27.7 (24.9; 31.3)	28.4 (25.1; 31.7)	27.7 (24.6; 31.2)	0.391	0.863
SBP (mmHg)	150 (139; 165)	150 (138; 167)	152 (140; 167)	150 (139; 162)	0.357	0.366
DBP (mmHg)	92 (84; 100)	90 (82; 100)	92 (85; 101)	93 (84; 100)	0.244	0.283
Plasma aldosterone (ng/L)	189.5 (124; 286)	199 (140; 300.5)	204.5 (124; 321)	173 (116; 273.5)	0.014	0.075
PRC (U/L)	3 (2; 6.4)	3.15 (1.5; 6.2)	2.6 (1.8; 5.9)	3.2 (2; 6.8)	0.018	0.169
ARR (ng/U)	57.7 (26; 118.1)	69.5 (32.8; 140)	67.3 (24.9; 143.5)	47.1 (25.1; 100.3)	0.002	0.029
Na (mmol/L)	141 (139; 143)	142 (140; 143)	141 (139; 143)	141 (140; 143)	0.563	0.387
K (mmol/L)	3.6 (3.2; 3.9)	3.5 (3.2; 3.8)	3.5 (3.1; 3.9)	3.7 (3.4; 3.9)	<0.0005	0.001
Minimal K (mmol/L)	3 (2.7; 3.3)	2.9 (2.6; 3.1)	2.9 (2.7; 3.2)	3.1 (2.8; 3.3)	<0.0005	0.001
GFR (mL/min/1.73 m ²)	85 (71.4; 97.7)	93.5 (77.3; 106.6)	86 (72.8; 97)	80.9 (67.2; 93)	<0.0005	<0.0005
Glucose (mg/dL)	99 (91; 109.3)	99 (90; 113)	99 (91; 110)	98 (92; 108)	0.434	0.8
HbA1c (%)	5.3 (5.1; 5.7)	5.6 (5.3; 5.9)	5.4 (5.1; 5.7)	5.3 (5; 5.6)	<0.0005	0.006

Changes between three-year periods: Chi² trend test for categorical variables, Jonckheere-Terpstra trend test for quantitative variables. Sex-adjusted comparison of the trends: linear regression calculation for quantitative variables, logistic regression calculation for categorical variables. Bold values indicate significant changes.

AH, arterial hypertension; ARR, aldosterone to renin ratio; BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; DDD, defined daily dose; GFR, glomerular filtration rate; IFG, impaired fasting glucose; K, potassium; MI, myocardial infarction; Na, sodium; *n*, number; PA, primary aldosteronism; PRC, plasma renin concentration; SBP, systolic blood pressure; *y*, years.

Italian cohort (15.2%) (4). When compared to the Torino cohort, median plasma aldosterone levels were lower in our patients, as well in unilateral (plasma aldosterone: 432 vs 232 ng/L or bilateral cases 295 vs 163 ng/L), potentially indicating biochemically milder forms among our patients. However, these results need to be considered in the context of assay-specific characteristics and their different reference ranges (4).

In our analysis, we explored the patients in three time periods (2008–2010; 2011–2013; 2014–2016) in order to evaluate the evolution of secular trends. As expected, numbers of newly enrolled patients increased triennially with increasingly more female patients being identified. The age of PA diagnosis was significantly higher in men who generally tend to consult doctors later in life (24). With the introduction of a more widespread screening, unilateral PA patients remained the most commonly identified subgroup among our patient cohort. However, the relative distribution of subtypes over time changed in favor of

milder cases, similar to previously described findings (2). These findings are in accordance with overall lower DDD values, while median SBP and DBP values did not change, indicating a trend toward the increased rate of milder diagnosed PA cases, even among unilateral PA patients. This trend is again found in lower ARR values within the last three years among all groups. Correspondingly, median and minimal potassium values were higher over the course of the last three years, exemplifying a trend toward more normokalemic PA patients, a finding mirrored by the increase in normokalemic patients, in accordance with other publications on trends in PA diagnosis (1, 25).

Finally, we realized that the number of PA patients with noAVS subtype increased over time (from 6 to 24%). This trend might be driven by the fact that milder forms of PA have a low pre-test probability of APA and can often be well controlled by MRA therapy, thereby sparing the patient from adrenal venous sampling. Along the same line, initiation of MRA therapy without subtype

Figure 1

Relative distribution of PA subtypes – comparison over three time periods (2008–10 (I), 2011–13 (II), 2014–16 (III)).

Significant decrease of unilateral (I) vs (III): $P < 0.0005$, (II) vs (III): $P = 0.028$ cases over time. NoAVS: patients who did not undergo subtyping by AVS.

differentiation in all instances has been advocated for in the latest guidelines by the American Endocrine Society on PA when surgery is not desired by the patient or not feasible (5).

Figure 2

Upper panel: Median plasma aldosterone and ARR ratios over time (2008–2016). Lower panel: ratio of normokalemic to hypokalemic cases over time.

Strengths and limitations of the study

Our study is a retrospective study on prospectively collected data of patients included from six different centers that comprise the German Conn's Registry. It is one of the largest prospectively studied cohorts of PA patients. All patients underwent a standardized protocol in order to be classified into subgroups. A limitation of the study is the lack of comparison to patients with non-secondary arterial hypertension. Additionally, the assessed laboratory values need to be seen in light of assay heterogeneity, as the centers used different platforms. Furthermore, the vast majority of the enrolled patients were contributed by the Munich center, limiting a complete generalization of the results to other areas and centers (Supplementary Table 2).

Conclusions

Taken together, our results are in accordance with an increased screening intensity for PA in our centers. We identified a trend toward diagnosing milder forms of PA in recent years, translating into more normokalemic cases with higher potassium levels at diagnosis. In accordance with a recent publication, we suggest that further studies will be needed to assess the emerging question whether these milder forms of PA might not have an increased cardiovascular risk when compared to essential hypertension (26). Increasingly more female patients were identified, an underrepresented cohort: arterial hypertension is often underestimated and undiagnosed in women as there is an ongoing misperception that women are at a lower risk of cardiovascular disease than men (27). Especially younger patients and female patients particularly benefit in terms of biochemical and clinical remission rates from a favorable surgical outcome (18), in part due to differences in the mutational spectrum of adenoma driver mutations (28). These results should raise awareness to continue to screen for hypertension and PA in women with the same frequency as in men.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-17-0978>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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