ORIGINAL ARTICLE

The Diagnosis and Treatment of Primary Hyperaldosteronism in Germany

Results on 555 Patients From the German Conn Registry

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SUMMARY

Background: Primary hyperaldosteronism (Conn's syndrome) is being diagnosed increasingly often. As many as 12% of patients with hypertension have the characteristic laboratory constellation of Conn's syndrome. Its diagnosis and treatment have not been standardized.

Methods: The authors retrospectively analyzed data of 555 patients (327 men and 228 women, aged 55 ± 13 years) who were treated for primary hyperaldosteronism in 5 different centers from 1990 to 2006. The objective was to determine center-specific features of diagnosis and treatment.

Results: 353 (63%) of the patients had the hypokalemic variant of primary hyperaldosteronism; 202 never had documented hypokalemia. The centers differed markedly with respect to the patients' clinical presentation, diagnostic testing of endocrine function, and diagnostic imaging techniques, including adrenal venous sampling. The adrenalectomy rate ranged from 15% to 46%.

Conclusions: The registry data reveal an unexpected heterogeneity in the diagnostic evaluation and treatment of primary hyperaldosteronism. National or international guidelines are needed so that these can be standardized.

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Primary hyperaldosteronism (Conn's syndrome) has come to be viewed as the most frequent cause of secondary hypertension; according to recent studies it is found in 5% to 12% of patients with high blood pressure (1–4). Over a third of Europeans suffer from arterial hypertension (5), so around 1.5% to 3.5% of the European population are affected. At a conservative estimate, this corresponds to approximately 1.2 million people in Germany.

Aldosterone is thought to play a crucial part in the pathogenesis of cardiovascular diseases (6, 7). Patients with primary hyperaldosteronism have higher cardiovascular and cerebrovascular morbidity than those with essential hypertension and comparable blood pressure (6, 8).

The principal reason for the increasingly frequent diagnosis of this disease, once viewed as rare, is that normokalemic Conn's syndrome is now recognized as an independent disease entity. It is much more common than the "classic" pattern of primary hyperaldosteronism with hypertension, hypokalemia, and alkalosis (9). Around two thirds of the patients demonstrate bilateral adrenal hyperplasia requiring lifelong treatment with a mineralocorticoid antagonist. One third of cases involve an aldosterone-producing adenoma that necessitates adrenalectomy.

There is a lack of consistency in the literature with regard to the diagnostic tests required to confirm or rule out primary hyperaldosteronism (2, 10–14). *Figure 1a, b* shows the procedure that was recommended for the German-speaking countries in 2007 (10). If primary hyperaldosteronism is suspected, the first step is to determine the aldosterone:renin ratio (*figure 1a*), bearing in mind that numerous antihypertensive medications can influence this ratio and lead to incorrect results. Antihypertensives with a marked effect on the aldosterone:renin ratio should therefore be temporarily discontinued, if possible, and replaced by agents with a lesser effect, if the patient's blood pressure allows (10, 11).

If screening is repeatedly positive for primary hyperaldosteronism, a confirmatory test is obligatory. The saline load test is most commonly used to demonstrate the absence of aldosterone suppression; less frequently, the time-consuming fludrocortisone suppression test—

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FIGURE 1

Recommended diagnostic procedure in suspected primary hyperaldosteronism (according to 10)

- a) Screening for primary hyperaldosteronism and confirmation of diagnosis (according to 10). Because determination of plasma renin concentration (PRC) is now offered by most commercial laboratories and is simpler in the preanalytic phase (no storage on ice required before centrifugation in the laboratory), it is preferred to plasma renin activity (PRA). * Since there are various assays with relatively large differences in normal values for both PRC and plasma aldosterone concentration (PAC), it is crucial to heed the specifications (16, 21). Conversion factors: PAC: [ng/L] × 2.775 = [pmol/L]; PRC: [ng/L] × 1.66 = [mU/L].
- b) Differential diagnosis and treatment of primary hyperaldosteronism. PAC, plasma aldosterone concentration

regarded as gold standard—or the captopril test are employed (2, 11). The lasix-renin test shows low sensitivity and specificity and is thus no longer recommended.

After confirmation of the presence of primary hyperaldosteronism, diagnostic imaging of the adrenal glands is necessary (figure 1b). Magnetic resonance imaging (MRI) and computed tomography (CT) are of limited value, however, particularly in patients over 40 years of age: on the one hand, higher numbers of endocrinologically inactive adrenal masses are found with increasing age, while on the other, Conn's adenomas can be very small (<5 mm) and thus escape detection on imaging.

In addition, the posture test is used as a dynamic test to differentiate between an aldosterone-producing adenoma and bilateral adrenal hyperplasia. If the posture test shows decreased aldosterone and imaging demonstrates a circumscribed adrenal mass, an aldosterone-producing adenoma can be assumed. If the findings of the function test and diagnostic imaging are incongruent—as is the case in over 80% of patients—the next step is adrenal vein catheterization, the gold standard for differential diagnosis of the various subtypes (12, 14–16).

The frequency of primary hyperaldosteronism and the increased risk of cardiac, vascular, and metabolic complications underline the importance of a simple, universally available, and accurate scheme for identifying and properly treating those affected. The German Conn Registry was established in 2006 to evaluate the diagnosis and treatment of primary hyperaldosteronism in Germany and to document comorbid conditions and the disease course. The retrospective analysis presented in this article is based on data from 555 patients treated since 1990 in the participating centers. The aim of the study was to investigate a representative sample in order to establish criteria and biochemical and imaging procedures for diagnosis and classification of patients with Conn's syndrome in Germany.

The Conn Registry: structure, methods, and patient characteristics

The German Conn Registry (www.conn-register.de) was founded in Munich in March 2006 on the initiative of the German Endocrinology Society (DGE) and the GANIMED network (German Adrenal Network: Improving Medical Research and Education). The Conn Registry's database retrospectively and prospectively documents all patients with primary hyperaldosteronism treated in the participating centers from 1990 onward. The sole inclusion criterion is the presence of primary hyperaldosteronism. Patients with other causes of secondary hypertension are excluded.

Nine centers are currently involved:

- Charité, Berlin
- Endokrinologikum, Berlin
- Ruhr University, Bochum
- Department of Medicine, Ludwig Maximilian University of Munich (Medizinische Klinik Innenstadt and Institute for Prevention and Epidemiology of Circulatory Diseases)

TABLE 1

Patient characteristics by center (as of August 2007)

Center	Time of introduction of electronic patient archives	Center-specific diagnostic criteria for presence of Conn's syndrome	Number of patients	Proportion of hypokalemic patients ^{*2}	Blood pressure ^{*1} (mm Hg) (mean $\pm$ SD)	Number of anti-hypertensive medications ^{*1}	Number (%) of adrenalectomized patients in cohort
Ruhr University, Bochum	1999	1+2+3, 1+5/6	61	62%	165 $\pm$ 92	3.9 $\pm$ 1.9	22 (36%)
Charité, Berlin	1994	1+2+3, 2+3+5/6	53	72%	157 $\pm$ 93	2.8 $\pm$ 1.9	23 (44%)
University Hospital, Freiburg	1998	1+2+3, 1+5/6	79	69%	168 $\pm$ 100	2.4 $\pm$ 1.5	21 (27%)
University Hospital, LMU, Munich	1994	1+2, 1+3, 1+2+5/6	294	56%	169 $\pm$ 99	2.5 $\pm$ 1.7	45 (15%)
University Hospital, Würzburg	1999	1+2+3	68	84%	171 $\pm$ 101	3.1 $\pm$ 2.1	31 (46%)

^{*1}, on initial investigation; ^{*2}, defined as documented hypokalemia (potassium <3.5 mmol/L) not occurring during administration of diuretics, or requirement for potassium substitution; 1, pathological aldosterone:renin ratio; 2, serum aldosterone > mean normal range; 3, pathologic confirmatory test (saline load test, lasix-renin test, fludrocortisone test); 4, histological demonstration of adenoma after adrenalectomy; 5, blood pressure decrease after adrenalectomy; 6, blood pressure decrease after treatment with a mineralocorticoid antagonist SD, standard deviation

- University Hospital, Freiburg
- University Hospital, Würzburg (all 2006)
- University Hospital, Mainz (2007)
- University Hospital, Düsseldorf (2007)
- University Hospital, Dresden (2008).

By 2007 the first five of these institutions had provided 640 data sets. The other centers started recruiting later, so they had contributed no validated data sets by the time of the analysis presented here. This retrospective evaluation included patients treated at one of the centers up to the cut-off date of June 30, 2006.

Patients treated for a diagnosis of primary hyperaldosteronism were identified by means of electronic searches in databases (archives of doctors' correspondence, radiology findings, nuclear medicine) and inspection of medical record archives. Primary hyperaldosteronism was diagnosed on the basis of the typical laboratory constellation of an elevated aldosterone:renin ratio and other criteria such as function tests and response to treatment. These parameters were center-specific and were not standardized (table 1).

Information from the medical records that was relevant to the registry—going back as far as 1990—was documented pseudonymously in an Access database. These data comprised:

- Patient data
- Clinical and laboratory chemistry parameters
- Comorbidities
- Diagnostic and therapeutic procedures relevant to primary hyperaldosteronism.

The data were entered by trained staff using a standard electronic data input form. Duplications were excluded by data comparison. Eighty-five data sets were not included in analysis because of incomplete documentation

or implausible information. The data were analyzed using the R version 2.5.1 software.

Results

As of the time of evaluation (August 2007), comprehensive retrospective data on 555 patients had been entered in the Conn Registry. Figure 2 shows the distribution of these patients by age and sex. Their mean age was 55 years (standard deviation [SD] 13, range 17 to 89). Fifty-nine percent of the patients (327/555) were men, 41% (228/555) women (table 2). Taking account of repeated measurements, the patients' systolic and diastolic blood pressure at the time of initial investigation was 167 $\pm$ 29 mm Hg and 98 $\pm$ 18 mm Hg, respectively (mean $\pm$ SD).

Age and sex distribution of the patients documented in the Conn Registry

TABLE 2

Basic data on the patients in the Conn Registry (as of August 2007)

Basic data	
Total number of patients	555
Number of male patients	327 (59%)
Average age (years; mean±SD)	55±13
Systolic BP* ¹ (mm Hg; mean±SD)	167±29
Diastolic BP* ² (mm Hg; mean±SD)	98±18
Number of hypokalemic patients	353 (64%)
Duration of hypertension* ¹ (years; mean±SD)	12±10
BMI (kg/m ² ; mean±SD)	28±5

*¹, On initial investigation;

*², defined as documented hypokalemia (potassium <3.5 mmol/L) not occurring during administration of diuretics, or requirement for potassium substitution

Three hundred fifty-three patients (64%) showed a hypokalemic disease course, defined as documented hypokalemia (potassium <3.5 mmol/L) in the absence of diuretic treatment and/or the requirement for potassium substitution. The incidence of hypokalemia was independent of age. Men more frequently evinced a hypokalemic disease course than women (67% vs. 59%). The proportion of hypokalemic patients varied among the centers: 56% of those treated in Munich had a hypokalemic disease course, against 85% in Würzburg (*table 1*). The proportion of hypokalemic patients corresponded with the proportion of adrenalectomized patients: between 15% (Munich) and 46% (Würzburg) were subjected to surgery (*table 1*). Normokalemic and hypo-

kalemic patients showed only slight differences in blood pressure and number of antihypertensive medications (systolic 167 ± 30 mm Hg vs. 169 ± 31 mm Hg; diastolic 98 ± 17 mm Hg vs. 99 ± 18 mm Hg; mean number of antihypertensives 2.2 vs. 2.5).

From 1999 onward all centers possessed electronic databases that enabled comprehensive documentation of cases of primary hyperaldosteronism. The annual number of patients treated for the first time for primary hyperaldosteronism at the various centers rose slightly from this time, but the proportion of normokalemic patients stayed the same (*figure 3*).

Both the choice of function tests for confirmation of diagnosis and for differential diagnosis and the proportion of patients in whom such tests were employed varied widely among centers (*figure 4*): the lasix-renin test was carried out most frequently (in 32% of all patients), although its use was restricted to two centers.

The saline load test—the classic suppression test for confirmation of primary hyperaldosteronism—was performed at all centers (in 25% of patients overall); the proportion of patients investigated varied from 13% to 56% across the centers. Other tests for confirmation of the diagnosis of primary hyperaldosteronism (fludrocortisone suppression test, captopril test) were used in only 1% of patients whose cases were documented in the registry.

The type and number of diagnostic imaging procedures, together with adrenal vein catheterization, are shown in *figure 5*. Adrenal CT was performed in 55% of all patients, MRI in 33%. Selective sampling of adrenal venous blood was carried out in 32% of cases overall, with the proportion varying widely across the centers (from 19% to 84%).

Discussion

The classic constellation of spontaneous hypokalemia in a patient with high blood pressure arouses suspicion of Conn's syndrome. Most patients are then investigated and treated at a specialized facility. The principal reasons for this are the following:

- The complicated biochemical confirmation of the diagnosis
- The complex differential diagnosis
- The highly specialized laparoscopic adrenalectomy in the case of Conn's adenoma, performed only in particular centers.

Although no data are available for health services research, probably only a very small proportion of cases are managed at facilities other than university hospitals or specialist endocrinology practices. Therefore, the centers participating in the Conn Registry can be considered representative for the care of patients with primary hyperaldosteronism.

This study has the following limitations:

- The retrospective data acquisition
- The incomplete documentation of all patients before 1999
- The differing diagnostic criteria in the participating centers (*table 1*).

FIGURE 3

Annual number of patients with primary hyperaldosteronism treated for the first time at the centers contributing data to the Conn Registry. Seven patients documented before 1990 are included in the total for 1990.

A major strength of the study is that it is the first to analyze data from different centers in a standardized registry using a central database containing information on a very high number of patients.

Owing to a modified screening strategy, the majority of patients with primary hyperaldosteronism described in the recent international literature are normokalemic (4, 9, 17). Two modifications were principally responsible for this development:

- Use of the aldosterone:renin ratio, more sensitive than the classic biochemical criterion of suppressed renin in the presence of elevated plasma aldosterone
- Extension of screening from exclusively hypokalemic patients with hypertension to normokalemic hypertensives with only moderate pre-test likelihood of Conn's syndrome. This includes all treatment-resistant patients and untreated patients with grade 2 or 3 hypertension.

In the five participating centers, in contrast, the proportion of normokalemic patients stayed constant at ca. 35% over a 5-year period. This implies that in Germany it is still mainly hypokalemic patients who are investigated for Conn's syndrome. This contrasts with the development in some centers in Europe and elsewhere: In the most comprehensive review to date, Mulatero et al. analyzed the incidence of normokalemic primary hyperaldosteronism at 5 specialized hospitals across the world (in Italy, Australia, the USA, Singapore, and Chile) and found that the proportion of normokalemic patients ranged from 63% to 91% (18).

Comprehensive documentation of the cases of primary hyperaldosteronism in our cohort of patients treated at the centers participating in the Conn Registry can be assumed for the period from 1999. From this time onward, no essential increase was observed in the annual incidence of primary hyperaldosteronism in the data set analyzed here. The increase in cases by a factor of 1.3 to 6.3 (18, 19) described in other centers since extension of screening to all patients with hypertension, independent of potassium status, has not been reflected in Germany. Since it can be assumed that the patients documented in the Conn Registry are a representative sample of the patients treated for primary hyperaldosteronism in Germany, screening is currently restricted to hypokalemic patients; documentation of normokalemic cases is limited.

The proportion of hypokalemic patients varies strikingly among the centers involved in the Conn Registry (Munich 56%, Würzburg 85%). This discrepancy can be attributed to a variable screening strategy and differences in the patient populations, but also to differences in the diagnostic criteria (table 1). As illustrated in figures 4 and 5, a broad spectrum of tests were used with variable frequency to confirm the diagnosis and identify the subtype of disease. The data from the 5 German Conn Registry centers demonstrate that the diagnostic criteria employed in different institutions are by no means trivial, because considerable differences can be observed in treatment outcome.

The above-mentioned study by Mulatero et al. showed a higher proportion of patients with aldosterone-producing

FIGURE 4

The dynamic tests used at the individual centers. The ordinate shows the proportion of patients at each center in whom the given test was performed.

* Other dynamic tests: captopril test, fludrocortisone suppression test

adenoma in centers where adrenal vein catheterization was regularly performed (28% to 50% vs. 9%) (18). Selective adrenal vein catheterization is the gold standard in the differential diagnosis of Conn's syndrome. It is obligatory in most patients with confirmed Conn's syndrome because imaging and biochemical tests cannot differentiate with sufficient confidence between Conn's adenoma and idiopathic adrenal hyperplasia. The sensitivity and specificity of this procedure exceed 95% with

FIGURE 5

Performance of imaging procedures and adrenal vein catheterization at the individual centers. The ordinate shows the proportion of patients at each center in whom the given procedure was performed.

* AVC: Selective blood sampling by means of adrenal vein catheterization

successful blood sampling from the adrenal veins. Even in specialized centers the rate of successful catheterization of both adrenal veins is only 70% to 90%.

The Conn Registry data on the relevance of adrenal vein catheterization for the treatment outcome are in agreement with these findings. Bochum and Würzburg, the two centers with the highest rates of adrenal vein catheterization (84% and 63%), also had higher numbers of adrenalectomized patients than the other institutions (36% and 46%). Only one center, namely Charité Berlin, had a low proportion of patients who underwent adrenal vein catheterization (13%) but nevertheless a relatively high rate of adrenalectomy (44%).

The retrospective nature of data evaluation does not permit precise analysis of the factors responsible for the variability in the frequency of adrenalectomy in patients with Conn's adenoma. Apart from adrenal vein catheterization, the varying prevalence of hypokalemia in the screened populations likely played the most important part: in exclusively hypokalemic populations the rate of Conn's adenoma is 68% to 85%, against <30% in exclusively normokalemic populations (18). The present data from German centers highlight the need for uniform recommendations to standardize the diagnosis of Conn's syndrome.

Conclusion

There is distinct variability in the choice of diagnostic procedures for primary hyperaldosteronism and the frequency of their use among German institutions. To date, the disease has been diagnosed differently, and thus treated differently, in the centers contributing data to the Conn Registry. These differences make it difficult to compare the treatment outcomes at the different centers with each other or with data from the published literature. Comprehensive quality assurance can be achieved only by standardization of the diagnosis and treatment of primary hyperaldosteronism.

The study originated in the framework of the German Conn Registry.

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Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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Key messages

- Conn's syndrome is the most frequent secondary cause of arterial hypertension.
- This complex disease requires standardized procedures to avoid errors of diagnosis and treatment.
- The German Conn Registry currently includes data on 555 patients treated at 5 university centers between 1990 and 2006.
- Analysis of the Conn Registry data shows unexpected heterogeneity of the biochemical tests and imaging procedures used to confirm the diagnosis and plan the treatment of Conn's syndrome.
- Standardization of the diagnosis of Conn's syndrome in Germany is urgently required for quality management purposes.

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