Prevalence of primary hyperaldosteronism in resistant hypertension: a retrospective observational study

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Summary

Background Results of several studies published since 1999 suggest that primary hyperaldosteronism (also known as Conn’s syndrome) affects more than 10% of people with hypertension; however, such a high prevalence has also been disputed. Experts generally agree that resistant hypertension has the highest prevalence of primary hyperaldosteronism, on the basis of small studies. We aimed to assess the prevalence of primary hyperaldosteronism in a large group of patients with resistant hypertension.

Methods Patients with resistant hypertension (blood pressure >140/90 mm Hg despite a three drug regimen, including a diuretic) who attended our outpatient clinic were assessed for primary hyperaldosteronism. Serum aldosterone and plasma renin activity were determined and their ratio was calculated. Patients with a positive test (ratio >65.16 and aldosterone concentrations >416 pmol/L) underwent salt suppression tests with intravenous saline and fludrocortisone. Diagnosis of primary hyperaldosteronism was further confirmed by the response to treatment with spironolactone.

Findings Over 20 years, we studied 1616 patients with resistant hypertension. 338 patients (20.9%) had a ratio of more than 65.16 and aldosterone concentrations of more than 416 pmol/L. On the basis of salt suppression tests, 182 (11.3%) patients had primary hyperaldosteronism, and response to spironolactone treatment further confirmed this diagnosis. Hypokalaemia was seen only in 83 patients with primary hyperaldosteronism (45.6%).

Interpretation Although the prevalence of primary hyperaldosteronism in patients with resistant hypertension was high, it was substantially lower than previously reported. On the basis of this finding, we could assume that the prevalence of primary hyperaldosteronism in the general unselected hypertensive population is much lower than currently reported. Thus, the notion of an epidemic of primary hyperaldosteronism is not supported.

Funding None.

Introduction In the decades after Jerome Conn’s initial description of the condition,1 the prevalence of primary hyperaldosteronism—increased aldosterone secretion from the adrenal glands—has remained an unresolved issue.2-3 Conn himself suggested that as many as 20% of people with hypertension could have this disorder; however, the ability to confirm this theory was hindered by the scarcity of widely available assays for renin and aldosterone determination.

For more than three decades primary hyperaldosteronism was thought to be a rare disease, diagnosed only in academic institutions by interested clinicians; studies of unreferred patients supported a prevalence of around 1%.4-7 By contrast, several studies published since 1999 suggest that the prevalence of primary hyperaldosteronism is about 10% of the population of patients with hypertension.8-13

The aldosterone to renin ratio (ARR) can be used as the screening test for primary hyperaldosteronism. However, its use is accompanied by a high percentage of false positive results, especially in patients taking β blockers, mainly due to methodological problems in accurate detection of low renin concentrations. Thus, a confirmatory salt suppression test is needed for an accurate diagnosis. From all available tests, the acute 4-h intravenous saline loading14 and the 4-day fludrocortisone administration15 seem to be the most reliable and offer accurate diagnosis of primary hyperaldosteronism.

Although there is still debate, most researchers agree that resistant hypertension is the condition with the highest probability of primary hyperaldosteronism detection.1,2,4-17 The true prevalence of resistant hypertension is unknown. Although some studies estimated the prevalence as between 2.9% and 13%,18 other observational studies and outcome trials have suggested that up to 30% of patients with hypertension could be resistant to therapy.19 The aim of our study was to contribute the 20-year data of our clinic, reporting the prevalence of primary hyperaldosteronism in a large white population of patients with resistant hypertension.

Methods We did a retrospective, observational study at the Hypertension Clinic of the Second Propedeutic Department of Internal Medicine, in Thessaloniki, Greece.
The study was done in accordance with the principles of the Helsinki declaration and the procedures followed were in accordance with institutional guidelines. The study was approved by the Hospital Ethics Committee and all patients gave written informed consent.

The study included all consecutive patients with resistant hypertension that attended our outpatient clinic over the past 20 years. Our definition of resistant hypertension included the presence of a diuretic in a three-drug regimen in full doses, without achievement of goal blood pressure (<140/90 mm Hg), as recommended by both the 2003 JNC7 report and the 2007 European guidelines. Despite the retrospective nature of the study, our belief that volume overload plays a crucial role in resistant hypertension led us to use diuretics in these patients since the beginning of the study. All patients fulfilled the current criteria of resistant hypertension. All patients with white-coat hypertension, revealed either by home blood pressure measurement in 589 of 2013 patients (29·3%) or ambulatory blood pressure measurement in 97 of 289 patients (33·6%), were excluded from the study. Thus, from a total of 2302 patients initially assessed for resistant hypertension, only 1616 patients were finally found to have resistant hypertension and were included in the study (figure 1).

All tests were done on an outpatient basis, except in susceptible high-risk patients (coronary heart disease or recent stroke) who were admitted to our Department. Antihypertensive drugs affecting ARR were stopped. Diuretics were discontinued for at least 4 weeks, whereas the other drugs (ACE-inhibitors, angiotensin receptor blockers, β blockers, calcium antagonists, and centrally acting drugs) were discontinued for at least 2 weeks. If drug withdrawal was deemed dangerous, patients were put on α blockers (prazosin and later terazosin, 524 patients [32·4%]), calcium antagonists (317 patients [19·6%]), or their combination (189 patients [11·7%]). This approach was adopted because β blockers suppress renin activity resulting in false positive ARR results, whereas diuretics and the other agents result in false negative results. When hypokalaemia (serum potassium less than 3·5 mmol/L) was observed, it was corrected by potassium supplementation before ARR determination, and dietary salt intake was liberal throughout the diagnosis workup.

All tests were done during morning hours in a quiet room under steady conditions. Plasma renin activity and serum aldosterone were measured in blood samples both obtained after a 2 h rest in supine position (0800–1000 h) and after 1 h of ambulation (1100 h).

Patients with high ARR and high serum aldosterone were given salt loading suppression tests (acute 4 h intravenous saline loading and 4-day fludrocortisone administration), to confirm or exclude the diagnosis of primary hyperaldosteronism. Intravenous administration of two litres saline in 4 h (acute salt load) was followed by 4 days of fludrocortisone 0·1 mg every 6 h.

<table>
<thead>
<tr>
<th>Study population</th>
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<tbody>
<tr>
<td><strong>Age (years), mean (SD)</strong></td>
<td>55·8 (13·3)</td>
</tr>
<tr>
<td><strong>Men, n (%)</strong></td>
<td>824 (51%)</td>
</tr>
<tr>
<td><strong>Body-mass index (kg/m²), mean (SD)</strong></td>
<td>31·3 (6·8)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg), median (IQR)</strong></td>
<td>154 (132–284)</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mm Hg), median (IQR)</strong></td>
<td>101 (64–138)</td>
</tr>
<tr>
<td><strong>Heart rate (beats per min), median (IQR)</strong></td>
<td>75 (48–120)</td>
</tr>
<tr>
<td><strong>Potassium (mmol/L), median (IQR)</strong></td>
<td>4·2 (2·0–5·2)</td>
</tr>
<tr>
<td><strong>Previous medication, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>1616 (100%)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>1263 (78%)</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>1170 (72%)</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>737 (46%)</td>
</tr>
<tr>
<td>β blockers</td>
<td>634 (39%)</td>
</tr>
<tr>
<td>α blockers</td>
<td>128 (8%)</td>
</tr>
<tr>
<td>Centrally acting drugs</td>
<td>115 (7%)</td>
</tr>
</tbody>
</table>

Table 1: Clinical and biochemical characteristics of total study population (n=1616)
on a high sodium diet and potassium supplementation as needed.

Adrenal CT scanning was done for localisation purposes; the results, however, were considered only indicative, since this approach could be misleading. Although adrenal vein sampling was done in some patients for differentiation between adenoma and primary hyperplasia, this test was not done in all patients because of technical difficulties.

The diagnosis of primary hyperaldosteronism was further confirmed by the response to spironolactone (400 mg a day gradually tapered to 12.5–50 mg according to blood pressure response). This confirmatory therapeutic criterion is different from the currently reported good response to spironolactone addition of patients with resistant hypertension, since we did not add spironolactone to previous therapy but instead withdrew all previous medications and assessed the response to spironolactone monotherapy. Patients not controlled with spironolactone monotherapy after tapering received additional drug treatment in order to achieve target blood pressure.

Blood pressure was measured using standard methods with a mercury sphygmomanometer. Serum aldosterone and plasma renin activity were measured with commercial radioimmunoassay kits.

Statistical analysis

Analysis was done with the Statistical Package for Social Sciences version 16 for Windows. Results are expressed for continuous variables with a normal distribution as mean (SD) and with non-normal distributions as median (IQR). Qualitative variables are expressed as frequencies. Kolmogorov-Smirnov algorithm was used to determine whether each variable had a normal distribution. Independent Student’s t test or Mann-Whitney U test was used to estimate differences between mean values of two independent groups. Paired Student’s t test or one-way repeated measures ANOVA, as parametric alternatives, and the Wilcoxon signed-rank test or the Friedman test, as non-parametric alternatives, were used for repeated measurements of the same variable on two (t test, Wilcoxon) or three (ANOVA, Friedman) different time points. Comparison of frequencies was done by Pearson χ² test with the Yates correction where appropriate (continuity correction was used to improve the fit to the exact probability).

Role of the funding source

There was no funding source for this study. SD, KP, MD, and CZ had full access to the data in the study and made the final decision to submit for publication.

Results

Over 20 years, 1616 patients with truly resistant hypertension were studied in our Department. The baseline characteristics of the patients are shown in table 1. Hypokalaemia was detected in 311 (20.5%) patients with resistant hypertension.

A positive test, defined as the combination of a high aldosterone to plasma renin activity ratio (more than 65.16) and serum aldosterone concentrations of more than 416 pmol/L was seen in 338 patients (20.9%)—ie, one in five patients with resistant hypertension had a positive ARR test; hypokalaemia was present in 117 (34.6%) of these patients.

All 338 patients with a positive ARR test were given suppression tests. The acute saline loading test was regarded as positive when serum aldosterone levels did not fall below 222 pmol/L at the end of saline infusion. The fludrocortisone test was regarded as positive when serum aldosterone levels were higher than 139 pmol/L after fludrocortisone administration (figure 1).

From the findings of salt suppression tests, primary hyperaldosteronism was diagnosed in 182 patients (53.8% of patients with positive ARR and 11.3% of the total study population)—ie, one in ten patients with resistant hypertension had primary hyperaldosteronism. Since we have given suppression tests only to patients with a positive ARR test (ARR of more than 65.16 and serum aldosterone more than 416 pmol/L), the validity of the sensitivity and the specificity of this test is limited. For the acute salt loading test, the sensitivity was 97.3% (95% CI 93.4–98.9) and the specificity was 80.1% (95% CI 72.8–85.9). The fludrocortisone test was used as the gold standard since it provided identical results with the response to spironolactone.
Figure 2: Blood pressure levels before and after spironolactone therapy in patients with primary hyperaldosteronism either on monotherapy or combination therapy.

Patient characteristics are shown in table 2. Systolic and diastolic blood pressure were significantly higher in patients with primary hyperaldosteronism than in those with essential hypertension. Serum aldosterone concentrations of patients during the acute saline loading test and fludrocortisone test are also shown in table 2. Hypokalaemia was noted in 83 patients (45.6%), and its frequency was significantly higher (p<0.0001) than in patients without primary hyperaldosteronism (15.9%).

Diagnosis of primary hyperaldosteronism was further confirmed by the response to spironolactone treatment. Hypokalaemia was corrected, and both systolic and diastolic blood pressure were significantly reduced within the first 2–4 weeks of spironolactone administration compared with pretreatment levels (figure 2). All patients achieved target blood pressure, but spironolactone was gradually tapered to 12.5–25 mg, partly to avoid gynecomastia. Thus, most of our patients were on additional antihypertensive treatment and only 68 patients (37.3%) were on spironolactone monotherapy.

Discussion

Although the ARR was positive in about 20% of patients with resistant hypertension, after three confirmatory tests the diagnosis of primary hyperaldosteronism was confirmed only in about half, resulting in a prevalence of 11.3% of the total study population. Thus, only one in ten patients with resistant hypertension was finally diagnosed as having primary hyperaldosteronism. If we take into account that resistant hypertension is seen in 10–30% of people with hypertension, we could reasonably assume that primary hyperaldosteronism is substantially less common in patients with hypertension than currently thought. Primary hyperaldosteronism would therefore be a tertiary endemic (at specialised referral centres in tertiary hospitals) rather than a primary epidemic disorder.

A substantial number of specialists believe that primary hyperaldosteronism represents by far the most common form of secondary hypertension and affects more than 10% of unselected hypertensive patients. However, results obtained from high prevalence studies could be biased because patients with hypertension were generally recruited from specialist referral centres. The observed high prevalence might be specific to the tertiary care centres and indicate the highly selected nature of referred patients. Despite all precautions that were taken in a multicentre trial, heterogeneity of primary hyperaldosteronism prevalence was seen between different centres, suggesting possible occurrence of referral bias.

Furthermore, accurate confirmation of primary hyperaldosteronism with appropriate suppression tests was not always done. The relevance of these prevalence studies to general practitioners dealing with patients with hypertension might therefore be questioned. Such limitations in existing studies can generate scepticism about the epidemic form of primary hyperaldosteronism and several hypertension experts have expressed their concerns.

Our data suggest that primary hyperaldosteronism has been over-represented in patients with resistant hypertension. In five previous studies, the prevalence of primary hyperaldosteronism ranged from 14% to 23%. However, these studies included a small number of patients, with a total sample of 418 patients. When our data were combined with the data from these five previous studies using a fixed effects model, the pooled weighted average of primary hyperaldosteronism prevalence in resistant hypertension was estimated at 12.3% (95% CI 10.8–13.6). However, since the heterogeneity between studies was high (Q=13.56, variance τ²=0.0015) we have also used a random effects model and the pooled weighted average of prevalence was 15.75% (95% CI 11.6–19.9).

The aldosterone-dependent cardiovascular morbidity is the main factor that justifies cost-effectiveness of the increased efforts of case finding. Several studies have shown that patients with primary hyperaldosteronism could be at higher risk for target organ damage (greater left ventricular mass, reduced diastolic function, increased arterial wall stiffness, higher urinary albumin excretion rate, and partially reversible renal dysfunction) than patients with essential hypertension. Patients presenting with either adenoma or idiopathic hyperplasia causing primary hyperaldosteronism had a significantly higher rate of cardiovascular events (myocardial infarction, stroke, atrial fibrillation) than the matched
essential hypertensive patients.” Indeed, a recently published study reported that the prevalence of cardiovascular events (coronary heart disease, cerebrovascular events, arrhythmias) was greater in primary hyperaldosteronism (35%) than in essential hypertension (11%; odds ratio 4·61; 95% CI 2·38–8·95; p<0·001); older age and longer duration of hypertension were independently associated with the cardiovascular endpoints, whereas the cardiovascular outcome was similar in patients with primary hyperaldosteronism managed either with adrenectomy or aldosterone antagonists.31

An important finding of our study is the high percentage of false positive ARR results. Nearly half of our patients with a positive test did not have primary hyperaldosteronism; a finding which is in line with previous reports that 30–50% of patients with a positive ratio have aldosterone levels that are normally suppressed after further confirmatory testing.16–20 Therefore, other screening tests with fewer false positive results or improvement of existing ones are needed in order to obtain solid reproducible results that will substantially reduce the number of patients who will undergo unnecessary suppression testing.

Another notable finding is the low frequency of hypokalaemia, which was detected in less than half the patients (45·6%). The majority of studies published since 2002 have shown that most patients with primary hyperaldosteronism have baseline potassium blood levels within the normal range and that hypokalaemia is uncommon.32,33,37,38,24 Our data support the opinion that, although hypokalaemia is a useful indicator of primary hyperaldosteronism, we cannot rely on its occurrence to indicate this secondary form of hypertension, since the diagnosis will be missed in more than half the patients with primary hyperaldosteronism.

The retrospective nature of our study has limitations compared with prospective trials; however, every effort was made to provide high quality data. All consecutive patients with resistant hypertension attending our centre were included in the study, after exclusion of patients with white-coat hypertension. All patients fulfilled the current criteria of resistant hypertension. Moreover, the data were monitored, collected, entered and processed in the database, and analysed by an investigator (a biologist) blinded to clinical data, final diagnosis, and treatment decisions.

In conclusion, the prevalence of primary hyperaldosteronism in patients with resistant hypertension in our study was lower than that reported in smaller studies. Based on the prevalence of patients with resistant hypertension in the general hypertensive population and the lower prevalence of primary hyperaldosteronism in milder forms of hypertension, we could assume that the prevalence of primary hyperaldosteronism in the general unselected hypertensive population is much lower than currently thought. Our findings therefore do not support the notion of an epidemic form of the condition, suggesting that its high prevalence in other studies could be attributed to selected populations in tertiary centres. Nevertheless, the cardiovascular consequences of primary hyperaldosteronism justify the active search for this disorder in patients with resistant hypertension. ARR has a low positive predictive value, and so needs either improvement or substitution by a more robust and reliable screening test. Hypokalaemia, in line with other studies, was absent in more than half of patients with primary hyperaldosteronism and therefore is not a requisite for diagnosis. Further studies in unselected populations are needed to accurately estimate the prevalence of primary hyperaldosteronism within the general population of patients with hypertension.

Contributors
SD, KP, MD, and CZ conceived the idea and design of the study, participated in all steps of study conduct, data verification, and authorship, and had the final decision to submit the paper for publication. PP, AT, NK, and NP participated in the testing. KV participated in data collection, processing, and analysis. All authors have seen and approved the final version of the manuscript.

Conflict of interest statement
We declare that we have no conflict of interest.

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References


