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Primary aldosteronism: from case detection to histopathology with up to 6 years of follow-up

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The authors aimed to investigate the clinical characteristics, accuracy of diagnostic tests, and long-term outcomes after interventions in patients diagnosed with primary aldosteronism (PA) in Iceland throughout 5 years. A retrospective chart review was performed for all patients diagnosed with PA during the years 2007–2011 at Landspitali Hospital in Iceland, a referral center for the whole country. Workup after detection included salt loading test, positional test, computed tomography, and adrenal vein sampling. Patients with unilateral disease were offered treatment with adrenalectomy. A total of 33 patients were diagnosed with PA during the study period: 17 patients with bilateral disease and 16 with unilateral disease. Results from salt loading test were positive in 90% of patients. In patients with adenoma, 36% were responsive on their positional test and computed tomography scan showed a nodule in 73%. All patients with unilateral disease had a lateralization index ≥3. After surgery, patients had lower systolic blood pressure (P<.001) and number of hypertensive medications (P<.01).

1 | INTRODUCTION

Primary aldosteronism (PA) is a common cause of secondary hypertension (HTN).[1,2] Prospective and cross-sectional studies have reported the occurrence of PA in the hypertensive population to be 1% to 13%[3,4] and even up to 22% in select populations.[5] In addition to the negative effects of HTN, patients with PA have a higher risk of cardiovascular events compared with patients with primary HTN[6–8] and more often diabetes mellitus.[9,10] Generalized anxiety disorder has been reported to be more frequent in patients with PA compared with patients with primary HTN and they have been found to have decreased quality of life.[11] Thus, the morbidity of PA is exceedingly higher than that of primary HTN. PA can be caused by bilateral adrenal hyperplasia (BAH), unilateral aldosterone-producing adenoma (APA), unilateral hyperplasia as well as more rare conditions such as glucocorticoid remediable hyperaldosteronism.[12] After confirmation of PA, adrenal vein sampling (AVS) is the recommended method to diagnose unilateral vs bilateral disease in clinical guidelines.[5,13] The unilateral forms are treated with adrenalectomy while bilateral forms are treated with medications antagonizing the aldosterone action.[14] The new guidelines from the Endocrine Society and others have demonstrated the challenge in diagnosing PA and the debate regarding all steps of the workup process.[14–18] In an effort to simplify this expensive workup process, researchers have suggested that a "first look" with plasma renin activity could decide upon further investigations for PA[19] and others have challenged the need for confirmatory testing.[20] The aim of this study was to investigate the clinical characteristics, accuracy of diagnostic tests, and long-term outcome after interventions in patients diagnosed with PA at our institution after starting a structured workup protocol with verification tests, computed tomography (CT) of the adrenals, and AVS.

2 | MATERIALS AND METHODS

A retrospective chart review was performed of all patients (18 years and older) diagnosed with PA during 2007–2011 at Landspitali University Hospital (LUH) in Iceland, a referral center for the whole

country (population of 330 000 people). LUH is the only place in the country where AVS is performed. A structured workup for diagnosing PA was started in 2007 at LUH and all patients were then diagnosed using the same standardized methods. Patients were all referred to the same endocrinologist for various reasons, resistant HTN, a nodule on adrenal CT in patients with HTN, or HTN with hypokalemia. The same endocrinologist followed all of the patients from case detection to diagnosis of PA and through at least yearly follow-up after diagnosis. The same interventional radiologist performed all AVS and the same surgeon performed all endoscopic adrenalectomies during the study period.

In each visit to the hospital during the diagnostic workup process, the patient's systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in a sitting position. Serum potassium (s-potassium) levels were measured, the need for potassium supplementation evaluated, and the number and type of hypertensive medications (HTMs) documented. HTN medication did not include aldosterone-blocking agents in the workup process. After PA diagnosis and AVS, HTMs could include aldosterone-blocking agents.

2.1 | Case detection

Patients were taken off HTMs that interfered with the renin-angiotensin-aldosterone system 4 to 6 weeks prior to planned screening and confirmatory tests. Serum aldosterone (s-aldosterone), 24-hour urinary aldosterone concentration (24hU-aldosterone), and direct renin concentration (DRC) in plasma were than measured. The cutoffs that were used as a reference were s-aldosterone >430 pmol/L[5] and 24hU-aldosterone >25 μg/24 h. For the DRC, the upright reference values from the manufacturer were 5.1 to 38.7 ng/L for patients aged 20 to 40 years and 1.8 to 59.4 ng/L for those aged 40 to 60 years, supine values were 3.6 to 20.1 ng/L for those aged 20 to 40 years, and 1.1 to 20.2 ng/L for those aged 40 to 60 years.

2.2 | Verifying test

Intravenous salt loading test (SLT) was used to confirm the diagnosis.[21] After a 10-hour bed rest, s-aldosterone, s-renin, and s-potassium were measured at 8 AM. An infusion of 2 L of 0.9% normal saline (NS) solution was then started and given over a 4-hour period, without standing up in between. After 4 hours of infusion, s-aldosterone, DRC, and s-potassium were measured again. The test was considered positive when s-aldosterone was >140 pmol/L[15,16] after the infusion. Normal potassium levels were ensured during the test by confirmation of s-potassium the night before, at the start of the infusion, and at the end of the test. If s-potassium levels on the night before the test were below normal, potassium supplementation was increased as needed.

2.3 | Subtype classification

Positional test (PT) was used for subtype classification. S-aldosterone, s-renin, and s-potassium were measured after 10-hour bed rest at 8 AM and again after 4 hours of standing. Patients were divided into two groups: responsive and unresponsive. S-aldosterone levels were considered responsive to posture when the upright s-aldosterone level was increased >50% compared with the recumbent level, and unresponsive to posture when the upright s-aldosterone level was <50% higher, or lower than the recumbent level.[16]

2.4 | CT scan and adrenal venous sampling

Patients with verified PA according to the results from screening, SLT, and PT were further examined with a CT scan and AVS to assess for unilateral vs bilateral disease. The CT scans were conducted with Philips Brilliance 64-slice CT (Amsterdam, Netherlands). At least an hour before the AVS, patients were started on a synacthen infusion of 93.75 μg/h (Synacthen [tetracosactrin], 0.25 mg/1 mL; Novartis Pharma, Rueil-Malmaison, France). A total of 3 mL of the synacthen solution was diluted in 800 mL of NS. The AVS was then executed as described by Sigurjonsdottir and colleagues.[5] Samples for s-aldosterone and serum cortisol (s-cortisol) were drawn from the left and right adrenal vein and from the vena cava inferior. The s-aldosterone/s-cortisol ratios from the left and right adrenal vein were divided by the s-aldosterone/s-cortisol ratio from the vena cava inferior. In order to diagnose a unilateral overproduction of aldosterone, the sample from the dominant adrenal had to have a ratio of >1.4 and from the nondominant adrenal <1 and the dominant/nondominant ratio or lateralization index (LI) ≥3. In three patients, AVS was unsuccessful in the first attempt because of difficulties in accessing the right adrenal vein but the procedure was successful on the second attempt. In one patient diagnosed with bilateral disease it was not possible to access the right renal vein and the procedure was not repeated.

2.5 | Treatment

When AVS indicated unilateral disease, patients were offered a laparoscopic adrenalectomy. Patients with bilateral disease were offered specified pharmacological treatment with either nonselective (spironolactone) or selective (eplerenone) aldosterone receptors inhibitors (ARIs).

2.6 | Follow-up

Patients were followed at least yearly after the diagnosis. At each follow-up visit, the patients' BP was evaluated and the number of HTMs and need for potassium supplementation was recorded. HTM after diagnosis could include aldosterone inhibitors. If patients missed follow-up visits, a measurement of BP from the home setting was used when possible.

2.7 | Analytical methods

Coat-A-Count Radioimmunometric Assay (RIA) was used to measure serum and urinary aldosterone (Siemens, Los Angeles, CA, USA). To measure s-potassium, an ion-specific electrode was used (Vitros, Ortho-Clinical Diagnostics, Rochester, NY, USA). DRC was determined

using a two-site RIA (Renin III Generation, Cisbio Bioassays, Bedford, MA, USA).

2.8 | Data analysis and ethical issues

The outcomes from screening, verifying, and subclassification tests were described by using frequency measures and percentage. Comparison between patients with adenoma and BAH using continuous variables was conducted with an unpaired Student *t* test. For each patient, the mean of available BP measurements was used to present the patients' BP prior to surgery or ARI treatment. The available measurements were taken at first visit to the endocrinologist and at each visit to the hospital during the diagnosis workup process. A mean value of the patients' BP at 1 and 2 years, 3 and 4 years, and 5 and 6 years of follow-up was used for the statistical analysis model. The mean BP prior to surgery or treatment with ARIs was then compared with the same patient's mean BP at 1 to 2, 3 to 4, and 5 to 6 years of follow-up. SBP and DBP values were compared separately and patients with unilateral and bilateral disease were compared separately. The same method was used for the comparison of number of HTMs before and after surgery or ARI treatment. A linear mixed effect model was used for these comparisons. A two-sided *P* value <.05 was considered statistically significant. All statistical analysis was performed with R version 3.1.1. (R foundation for Statistical Computing, Vienna, Austria).

Approval was obtained from the science ethical committee at the LUH and The Icelandic Data Protection Authority.

3 | RESULTS

Thirty-three patients were diagnosed with PA during the 5-year study period: 16 with unilateral and 17 with bilateral disease. All 16 patients with unilateral disease underwent an endoscopic adrenalectomy. Histopathology found 11 of 16 patients with cortical adenomas and four with hyperplasia. Patients' demographics are described in Table 1.

Results from the screening process showed that all patients had either elevated morning s-aldosterone >430 pmol/L or 24hU-aldosterone >25 μg. Three of the 16 patients (19%) with unilateral disease did not have s-morning aldosterone >430 pmol/L (data not shown). The mean DRC was 3.3±2.3 ng/L after 15 minutes of sitting in a chair in patients with adenoma and 9.6±8.1 ng/L in patients with bilateral disease (Table 2).

Results from SLT were positive in 28 (90%) of 31 patients (Table 2). SLT was repeated in two patients with a negative result because of high clinical suspicion. One of the patients had a positive test result after repetition (s-aldosterone 111 and 253 pmol/L after the first and second test) and the final diagnosis was adenoma on histopathology. The other patient had a negative test result for the second time. Three patients with negative SLT results continued the workup process due to high suspicion for PA and were diagnosed with bilateral disease (Table 3).

Two of the four patients with hyperplasia on histopathology were responsive to posture and 36% of the patients with adenoma.

In patients with unilateral disease, all except two (88%) had an LI ≥4 after AVS, who had an LI of 3 (Table 2).

In the unilateral group (n=16) there was a statistically significant improvement in SBP and decrease in the number of HTMs at follow-up compared with before adrenalectomy (*P*<.001 and *P*=.01, respectively) (Table 3). There was not a statistically significant difference in SBP, DBP, and number of HTMs at 5 to 6 years of follow-up between the unilateral and bilateral subgroups (data not shown). All patients with bilateral disease, except one, were started on treatment with ARI, 11 on eplerenone and five on spironolactone. Patients with both unilateral and bilateral disease did not need potassium supplementation after the interventions.

TABLE 1 Patient demographics

	Unilateral PA	Bilateral PA	*P* Value
Patients, No.	16	17	–
Male, No. (%)	12 (75)	7 (41)	–
Age, median (range)	57 (37–67)	51 (20–76)	–
SBP, mean±SD	161±23	150±22	.03
DBP, mean±SD	96±15	85±13	.001
HTMs, mean±SD	2.9±1.0	1.8±1.2	<.001
k+ Supplementation, No. (%)	14 (88)	8 (47)	–
Serum potassium[a]	3.5±0.4	3.8±0.3	.02
Disease distribution			
Adenoma	11	–	
Hyperplasia	4	–	
Inconclusive[b]	1	–	

Abbreviations: DBP, diastolic blood pressure; HTMs, hypertensive medications; PA, primary aldosteronism; SBP, systolic blood pressure.

[a]Serum potassium levels measured while patients were on potassium supplementation.

[b]Histopathology was inconclusive in one patient because the pathologist could not distinguish between hyperplasia and adenoma.

TABLE 2 Results from case detection, verification, and subtyping tests depending on patient's outcome with adenoma or BAH

	Adenoma (n=11)	BAH (n=17)	*P* Value
Morning serum aldosterone, pmol/L	1197±611	874±587	.15
24hU-aldosterone concentration, μg/L	44±17	34±12	.01
DRC, ng/L after 15 min of sitting	3.3±2.3	9.6±8.1	.008
DRC, ng/L after 10 h of bed rest	1.1±1.3	3.1±4.0	<.001
ARR, pmol/ng[a]	547±588	228±305	0.12
Serum aldosterone, pmol/L, after IV salt loading for 4 h	572±490	286±240	.08
Responsive to posture, No.	4/10	13/16	–
CT scan positive for nodule, No.	8/11	3/17	–
LI index after AVS	16±14	1.6±0.5	.009

Abbreviations: ARR, aldosterone/renin ratio; AVS, adrenal venous sampling; CT, computed tomography; DRC, direct renin concentration; BAH, bilateral adrenal hyperplasia; IV, intravenous; LI, lateralization index; 24hU-aldosterone; 24-hour urinary aldosterone.
[a]Recommended cutoff according to current guidelines from the Endocrine Society is 144 pmol/ng.[14]

TABLE 3 Demographics and results from case detection and subtyping tests in patients with negative results on salt loading test

	Patient 1	Patient 2	Patient 3
SBP, mm Hg	111	153	191
DBP, mm Hg	66	88	101
HTMs, No.	1	2	2
Potassium supplementation	Yes	No	No
Morning serum aldosterone, pmol/L	1331	632	596
24hU-aldosterone excretion, μg	50	30	35
DRC, ng/L	21	14	12
ARR, pmol/ng	63	45	49
PT before standing, serum aldosterone, pmol/L	387	429	167
PT after 4 h of standing, serum aldosterone, pmol/L	1185	1050	918
SLT	Negative	Negative	Negative
Aldosterone/cortisol ratio, left side[a]	4.7	2.6	
Aldosterone/cortisol ratio, right side[a]	5.1	3.4	4.8
LI index after AVS	1.08	1.13	–

Abbreviations: ARR, aldosterone/renin ratio; DBP, diastolic blood pressure; DRC, direct renin concentration; HTMs, hypertensive medications (patients were not treated with aldosterone inhibitors during the work up process); LI, lateralization index; PT, positional test; SBP, systolic blood pressure; SLT, salt loading test; 24hU-aldosterone, 24-hour urinary aldosterone.
[a]The aldosterone/cortisol ratio was calculated from each side after adrenal venous sampling (AVS).

4 | DISCUSSION

In this study we found 33 patients with PA after a structured diagnostic workup process that included screening tests, SLT, PT, CT scan, and AVS. A total of 16 patients were diagnosed with unilateral disease and 17 with bilateral disease. Unilateral hyperplasia was found in one fourth of patients with unilateral disease. All of the patients in our study had either elevated morning s-aldosterone or increased 24hU-aldosterone secretion at screening. We consider the 4-hour SLT to be an appropriate verification test, and AVS was vital for subtyping between unilateral and bilateral disease. Although PT and CT were not always reliable in subtyping these patients, they can serve as an important addition to the complicated diagnostic process. Patients with unilateral disease had significantly lower SBP and took fewer HTMs at 5 to 6 years of follow-up compared with before adrenalectomy.

In our study, all the patients had either elevated morning s-aldosterone >430 pmol/L or increased 24hU-aldosterone secretion >25 μg at case detection. Interestingly, three of the 16 patients (19%) with unilateral disease did not have s-morning aldosterone >430 pmol/L, which is in line with reports claiming that PA might be missed in the screening process if s-aldosterone values at 15 ng/mL (approximately 416 pmol/L) are used for cutoff.[22] Renin was not suppressed below reference cutoffs in all of our patients although the levels tended to be in the lower normal range. When patients arrived for screening they sat in a chair for 15 minutes before the sample was obtained. The renin manufacturer does not give reference values for

TABLE 4 Comparison of blood pressure and number of HTMs in patients with unilateral and bilateral PA, before and after adrenalectomy and ARI, respectively

Unilateral	Prior to Surgery	1 to 2 y Post-Op	3 to 4 y Post-Op	5 to 6 y Post-Op	*P* Value
SBP, mean±SD, mm Hg	161±18	145±20	144±18	135±10	<.001
DBP, mean±SD, mm Hg	96±12	88±10	90±12	90±11	.12
No. of HTMs, mean±SD	2.9±0.8	2.0±1.6	2.3±1.5	1.9±0.7	.01
Bilateral	**Prior to ARI**	**1 to 2 y After ARI**	**3 to 4 y After ARI**	**5 to 6 y After ARI**	***P* Value**
SBP, mean±SD, mm Hg	152±23	147±18	143±19	138±17	.17
DBP, mean±SD, mm Hg	85±11	88±10	88±12	87±7	.70
No. of HTMs, mean±SD	1.8±1.2	2.1±1.3	2.0±1.0	2.0±1.1	.09

Abbreviations: ARI, aldosterone receptor inhibitor; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation. A linear mixed effect model was used for the comparisons of blood pressure and number of hypertensive medications (HTMs; after diagnosis with adrenal venous sampling, these can include aldosterone inhibitors) prior to surgery and 1 to 2, 3 to 4, and 5 to 6 years after follow-up. Two-sided *P* value <.05 was considered statistically significant.

these situations, only supine and upright, used at our institution, and therefor these are difficult to interpret. There are many factors that can affect the renin and ARR values such as posture, time of day the sample is taken, age, ethnicity, and sodium intake.[14] Thus, we conclude that it can be important to take into account aldosterone in blood and urine as well as renin values when detecting patients for verification of PA.

Results from SLT were positive in all patients with unilateral disease but negative in three patients with a bilateral disease using the cutoff value of 140 pmol/L. There have been discrepancies in the literature regarding which confirmatory tests should be used as well as their sensitivity and specificity. Mulatero and colleagues[15] reported that supine SLT identified 88% of patients confirmed as having PA by fludrocortisone stimulation test (FST) when a plasma aldosterone concentration cutoff of 50 pg/mL (approximately 140 pmol/L) after SLT was used. Importantly, no patients with APA in their study were misdiagnosed with SLT, although in our study one patient with adenoma had negative SLT findings on his first test but positive findings when it was repeated. Another study found that supine SLT only identified 33% of patients diagnosed with PA by FST.[16] In these studies, the patients did not lie supine overnight as in our study, but from arriving as an outpatient in the morning. Three patients had negative SLT results in our study. Because they had a high morning s-aldosterone level, increased 24hU-aldosterone, and were responsive on their PT, they were further evaluated with AVS and finally diagnosed with a bilateral disease. This indicates the importance of clinical impression when choosing patients for confirmative and subtyping tests as there is not a single verifying test universally recognized with standardized cutoff values.

In this study, the PT was considerably accurate in subtyping patients with bilateral disease but not in subtyping patients with adenoma, as 36% of them were responsive to posture, which is in line with other reports.[23,24] There are very limited data on the results of PT in patients with unilateral hyperplasia. It is therefore interesting that we found these patients to be both responsive and unresponsive to posture.

The study did not find CT scans to be reliable for differentiating unilateral from bilateral PA, as three (18%) of the patients in the bilateral group had a nodule and only eight (63%) of the patients had adenoma. This is in accordance with other studies[25,26] that found CT to be unreliable in subtyping PA.

All patients with unilateral disease except two in our study had an LI ≥4. Those two patients had an LI of 3 and histopathology showed hyperplasia and adenoma, respectively. There is ongoing debate regarding the cutoff values for the LI. Young and colleagues[13] have reported that 96% of patients with APA and no patients with bilateral idiopathic PA had an LI ≥4, which is in accordance with our results. Recently, Umakosi and colleagues[18] showed that in hypertensive patients with a positive screening test but a negative confirmatory test for PA, no patient had an LI ≥4, supporting the correct diagnoses in our study.

Our study found the patients with unilateral disease (n=16) to have a significant reduction in SBP and number of HTMs postoperatively with up to 6 years of follow-up. This is in line with recent studies using AVS to accurately diagnose patients.[27,28] We did not see significant reductions in DBP and the majority of the patients still needed HTMs. The fact that HTN can persist after adrenalectomy has been reported in many studies.[28–32] Age, longer duration of HTN, and number of HTMs preoperatively are some of the factors suggested to explain this finding. Longer duration of HTN is an especially important factor as early diagnosis is critical to achieve the best response possible to treatment with adrenalectomy.[33] It is important to detect which patients need follow-up after surgery due to risk of relapse of PA. Recent studies using functional histochemistry are promising in that matter.[34,35] For example, Volpe and colleagues[36] reported that functional histochemistry changed the diagnosis in their study from unilateral adenoma to hyperplasia in six patients. One of our patients with adenoma had resistant HTN after surgery, and functional histochemistry might have given a different histopathology result. Further research is needed to better individualize the follow-up in PA patients.

The patients with bilateral disease in our study were younger than the patients with unilateral disease and the majority were women, both in contradiction with other reports.[37] The mean SBP in patients with bilateral disease decreased on average of 9 mm Hg before and after treatment with ARI (not significant). The small size of our group might affect the statistical insignificance. Bernini and colleagues[38] found treatment with ARI to significantly reduce BP in patients with

bilateral disease. Only 19 of 41 patients in that study were normotensive at follow-up and taking more HTMs than at diagnosis. Thus, our study is in line with others indicating the need for better BP control and more effective treatment in patients with bilateral disease. The need for potassium supplementation vanished both after treatment with surgery and after ARI, as others have reported.[38,39]

5 | STUDY LIMITATIONS

Our study population was relatively small; even so, these are complete results of patients diagnosed with SLT- and AVS-verified PA during 5 years, nationwide. It is important to note that this was not a screening study and therefore it is likely that more patients could been found with PA.[40,41]

6 | STUDY STRENGTHS

Even though this was a retrospective study, the data used were gathered prospectively and according to a predefined protocol at our institution. The same endocrinologist diagnosed and followed all of the patients, the same interventional radiologist performed the AVS, and the same surgeon executed all of the endoscopic adrenalectomies. In our study, we included all patients diagnosed with AVS-verified PA during the study period. Therefore, this is a population-based cohort for AVS-verified PA. Both patients with unilateral and bilateral disease were included in our study but many studies regarding PA only include patients with unilateral disease.

7 | CONCLUSIONS

In this nationwide study of AVS-verified PA during 5 years, unilateral PA was a usual cause of PA (48%) and unilateral hyperplasia was one fourth of that. We consider the 4-hour SLT to be an appropriate verification test, and AVS is vital for differentiating between unilateral and bilateral disease using an LI >3 as a reference point. Although PT and CT were not always reliable in subtyping these patients, they can serve as an important addition to the complicated diagnostic process. SBP and the number of HTMs needed was significantly reduced after surgery. Better indicators for individualizing follow-up after surgery are needed.

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CONFLICT OF INTEREST

All authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

GJ and HAS designed the study, and HAS was in charge of the execution of the study. GJ obtained data and performed the analyses. All authors were involved in the analyses and the interpretation of the results. All authors read, gave comments, and approved the final version of the manuscript. All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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