İstanbul Med J 2023; 24(1): 6-9
DOI: 10.4274/imj.galenos.2022.22309

Screening of Hyperaldosteronism on the Investigation of Secondary Hypertension: Single-centre Experience

Gülsüm Bingöl[1], Emre Özmen[2], Özge Özden[1], Leyla Bulut Arsoy[3], Yusuf Emre Uzun[1], Muharrem Nasifov[1], Esra Şüheda Hatipoğlu[4]

[1]Memorial Bahçelievler Hospital, Clinic of Cardiology, İstanbul, Turkey
[2]Siirt State Hospital, Clinic of Cardiology, Siirt, Turkey
[3]Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Biochemistry, İstanbul, Turkey
[4]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Endocrinology, İstanbul, Turkey

ABSTRACT

Introduction: Primary hyperaldosteronism (PHA), is a clinical syndrome that is defined as inappropriately increased serum aldosterone secretion and low plasma renin levels. PHA has been reported as the most common cause of secondary hypertension. In this retrospective study, we planned to show the significance of screening for this disease in hypertensive patients admitted to our clinic.

Methods: Our study included 64 patients who were admitted to our cardiology outpatient clinic between April 2018 and August 2021 with high blood pressure and were selected to be checked for plasma renin activity (PRA), PAC, and PAC/PRA ratios to exclude secondary hypertension. Medical records, hypertension treatments, and medical histories of the patients were reviewed from our hospital database.

Results: Of the 64 patients, 25 (39.1%) were female and 39 (60.9%) were male. After the first evaluation of the patients, 13 patients were decided to be assessed with the saline infusion test. PHA was diagnosed in 7 of 13 patients evaluated. In the adrenal MRI performed in 3 of 7 patients diagnosed with PHA, one adrenal hyperplasia and one adrenal adenoma were diagnosed in 2 different patients.

Conclusion: Primary hyperaldosteronism is one of the most important causes of secondary hypertension. Although there are various methods such as screening tests, the most commonly used method is the aldosterone/renin ratio and it is very practical to screen. Considering the various cardiovascular diseases that PHA is associated with, and the simplicity of treatment of PHA, we strongly believe that the screening threshold for PHA should be kept as low as possible and should be independent of age.

Keywords: Hyperaldosteronism, secondary hypertension, renin

Introduction

Primary hyperaldosteronism (PHA); is a clinical syndrome that is defined as inappropriately increased serum aldosterone secretion and low plasma renin levels. PHA has been reported as the most common cause of secondary hypertension; its prevalence was reported as 20% in patients with resistant hypertension, 10% in patients with severe hypertension, and around 6% in patients with uncomplicated hypertension (1,2). While plasma aldosterone level (PAC), plasma renin activity (PRA), and PAC/PRA ratio are used as a screening test for PHA; fludrocortisone oral sodium loading test, saline infusion test (SIT), or captopril tests are used to confirm the diagnosis (3). Jerome W. Conn, who was the first to define PHA, stated that the absence or low level of PRA and increased aldosterone secretion may be the first finding for the diagnosis of PHA rather than hypokalemia (4). Considering this information, it must be considered that in the presence of hypokalemia in hypertensive patients, the diagnosis of PHA should be suspected immediately, and it must be kept in mind that PHA can be seen in many patients without hypokalemia. In addition, screening for PHA is not as complex as it seems.

In this retrospective study, we planned to show the significance of screening for this disease in hypertensive patients admitted to our clinic.

Methods

Our study included 64 patients who admitted to the cardiology outpatient clinic between April 2018 and August 2021 with high blood pressure and were selected to be checked for PRA, PAC, and PAC/PRA ratios to exclude secondary hypertension. The patient group with a high probability of secondary hypertension consisted of young individuals with high blood

Address for Correspondence: Gülsüm Bingöl MD, Memorial Bahçelievler Hospital, Clinic of Cardiology, İstanbul, Turkey
Phone: +90 505 803 13 58 **E-mail:** bulut_gulsum@hotmail.com **ORCID ID:** orcid.org/0000-0001-5879-7866

Cite this article as: Bingöl G, Özmen E, Özden Ö, Bulut Arsoy L, Uzun YE, Nasifov M, Hatipoğlu EŞ. Screening of Hyperaldosteronism on the Investigation of Secondary Hypertension: Single-centre Experience. İstanbul Med J 2023; 24(1): 6-9.

Received: 04.08.2022
Accepted: 20.12.2022

pressure and individuals with resistant hypertension. Medical records, hypertension treatments, and medical histories of the patients were reviewed from our hospital database. Ethics committee approval was obtained from Memorial Bahçelievler Hospital Local Ethic Committee (approval number: 20, date: 13.09.2021). Written consent was obtained from all the patients. The blood pressure values and body mass index (BMI) of all patients were taken from the patient records.

The blood samples were taken from the patients for PAC and PRA between 08.00 and 09.00 a.m. in the morning with discontinuation of hypertension medication. The blood sample taken for PRA was taken into chilled tubes containing sodium ethylenediamine tetraacetate and centrifuged within the first 4 h after the sample was taken and stored in the freezer. PAC measurements were made with the aldosterone RIA kit (Beckman Coulter, Brea, CA). PRA measurements were made with an RIA kit (Beckman Coulter, Brea, CA) because of the production of angiotensin 1 *in vitro* in a pH 6.0 environment.

PHA screening test is considered positive in healthy and normotensive subjects; if PAC is over 75th percentile; PAC/PRC ratio is over 95th percentile, PAC >150 ng/dL, PRA <1 ng/mL/h, PAC/PRA ratio >30 (5-7). Patients with positive screening tests were evaluated by an endocrinologist. The SIT was performed to the patients who were considered suitable after the evaluation. After remaining in the supine position for at least 1 h before the start of the infusion, 2 L 0.9% saline was infused over a period of 4 h. Renin, aldosterone, and potassium levels were measured from the patients before and after the infusion. The diagnosis of PHA was confirmed in patients with a PAC value >10 ng/mL in the SIT after saline. Surrenal magnetic resonance imaging (MRI) was performed for the etiologic investigation of the patients whose diagnosis of PAH was confirmed by SIT.

Statistical Analysis

The data obtained because of the study were analyzed using the SPSS 24.0 program. Numerical values (age, systolic BP, diastolic BP, BMI, GFR, Na, K, Hb, and HbA1c, etc.) were given as minimum, maximum, mean, and standard deviation. Ordinal variables such as blood pressure, hospitalization complaint, smoking, and presence of hypertension were shown as percentages.

Results

Of the 64 patients included in the study, 25 (39.1%) were female and 39 (60.9%) were male. Demographic, clinical, and laboratory characteristics of the patients included in the study are shown in Table 1. The mean age of the patients was 40.9±13.8. Most of the patients (n=48, 75%) were admitted to the clinic with a complaint of high blood pressure. 8 (12.5%) patients were admitted to our clinic with complaints of headache, 3 (4.7%) patients with chest pain, and 5 (7.8%) patients with fatigue, dyspnea, facial flushing, drowsiness, and palpitations. There was no smoking history in 70.3% (n=45) of the patients. 37 patients (57.8%) had no history of additional disease, and 40 patients (62.5%) had no family history of hypertension.

Most patients participating in the study were not receiving any antihypertensive treatment. A small group of patients were multi-drug users and the drugs that may effect the result of the PAC, PRA, and PAC/PRA ratios were changed to those ones that had no effect on the abovementioned tests. Anti-hypertensive treatments used by the patients are given in Table 2.

Table 1. Clinical and labaratory features of patients

	n	Minimum	Maximum	Mean	SD
Age (y)	64	17.0	78.0	40.8	13.81
Systolic BP (mmHg)	64	110.0	220.0	147.5	18.01
Diastolic BP (mmHg)	64	60.0	120.0	91.8	9.86
BMI (kg/m^2)	64	20.2	38.1	27.5	3.90
GFR (mL/sec/1.7)	64	32.0	163.0	98.5	22.39
Na (mmol/L)	64	135.0	145.0	139.7	1.94
K (mmol/L)	64	3.4	5.2	4.3	0.35
Hb (g/dL)	57	9.4	18.6	14.2	1.77
HbA1c (%)	41	4.7	6.4	5.3	0.39

SD: Standard deviation, BP: Blood pressure, BMI: Body mass index, GFR: Glomerular filtration rate, Hb: Hemoglobin, HbA1c: Hemoglobin A1c

Table 2. Distribution of hypertensive drugs used by patients

Drug	n	%
ACEi	4	6.3
ARB	13	20.3
Beta blocker	13	20.3
Non-DHP CCB	2	3.1
DHP CCB	13	20.3
Diuretics	7	10.9

ACEi: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin 2 receptor blocker, non-DHP CCB: Non-dihydropyridine calcium channel blocker, DHP CCB: Dihydropyridine calcium channel blocker

Patients' PAC, PRA, and PAC/PRA ratios were evaluated by an endocrinologist. Because of this evaluation, it was decided to assess 13 patients with the SIT. PHA was diagnosed in 7 of 13 patients evaluated.

In the adrenal MRI performed in 3 of 7 patients diagnosed with PHA, one adrenal hyperplasia and one adrenal adenoma were diagnosed in 2 different patients, whereas no pathology was observed in the other patient.

Discussion

This study aimed to investigate the prevalence of PHA in outpatients with hypertension at our own institution and to determine the frequency of PHA diagnosis in patients without a classical PHA clinic.

PHA is a more common disease than previously thought, thanks to developing technology and research methods, although it was previously thought to be a rare cause of secondary hypertension. It has been shown that there is increased aldosterone secretion from one or both adrenal glands in the pathophysiology of PHA and that this release is independent of the primary regulators affecting aldosterone release. As a result, increased aldosterone binds to the epithelial sodium channel (ENaC) in the distal nephron, causing sodium retention and potassium excretion. Due to the sodium retained in the distal nephron, water retention increases and the classical findings in patients, such as hypertension, hypokalemia, and metabolic alkalosis, develop (8).

Different studies showed that PHA is closely associated with various cardiovascular diseases. Diseases such as coronary artery disease, atrial fibrillation, heart failure, and stroke are seen more frequently in patients with PHA patients (9-11). Therefore, it is critical to diagnose and treat PHA in terms of cardiovascular health.

Various studies have been conducted on the frequency of PHA in the community or among patients with hypertension and the prevalence varies according to the method used as a screening test. In a study by Monticone et al. (9), it has been demonstrated that because of a screening performed in 1700 hypertension patients, the screening test was positive in 14% of the patients. In addition, 6% of the patients were diagnosed with PHA when the confirmatory test was performed on these patients. In this study, serum aldosterone level >10 ng/dL and ARR >30 were determined as a screening test positivity criterion (9). In a study by Mosso et al. (12) in Chile, the prevalence of PHA was 6% in 609 hypertensive patients. In this study, ARR was accepted as >25 for screening test positivity.

Baudrand et al. (13), in a study of 241 mild-moderate hypertension patients, PRA <1 ng/mL/h; the prevalence of PHA was observed as 19% in patients with ARR >20 and aldosterone level >6 ng/mL. In our study, three different criteria positivity as PAC, PRA, and PAC/PRA (ARR) was accepted as "positive" as a screening test. and patients with ARR >30, PAC >150 ng/mL and PRA <1 ng/mL/h were evaluated further. Because of our study, the prevalence of PHA was observed to be 10.9%. The reason why our results differ from these studies; may be that our study did not adhere to a single criterion and the study population was small.

The most commonly known clinical features of PHA are hypertension, hypokalemia, and metabolic alkalosis, defined as the Conn triad. However, these three findings may not always be observed together in patients with PHA patients. In a multicenter study by Mulatero et al. (14), it was reported that hypokalemia was observed in 9-37% of patients diagnosed with PHA in the screening test for PHA in hypertensive patients. In another study by Käyser et al. (15), it was reported that all 343 hypertensive patients diagnosed with PHA in the screening were normokalemic.

In our study, all the patients diagnosed with PHA were normokalemic as well. PHA can also be observed in normotensive patients. In a study by Markou et al. (16), fludrocortisone-dexamethasone suppression test was performed in 100 normotensive patients independent of the baseline ARR rate, and the diagnosis of PHA was reached in 13% of these patients. In another study, Baudrand et al. (13) performed an oral sodium suppression test on 210 patients with normotensive but low renin activity (<1 ng/mL/h) and found the prevalence of PHA to be 14% (17). As shown in our study and other studies, the presence of classical clinical findings in patients should not be expected for PHA screening, and a screening test for PHA should be performed even in the absence of hypokalemia, particularly in patients with resistant hypertension. Although there is no specific age range for PHA screening in secondary hypertension in the established guideline, it is observed that clinicians mostly screen for PHA in young patients. Looking at the literature, there is no study investigating the presence of PHA in elderly (>65 y) hypertensive patients. However, considering that a patient diagnosed with PHA in our study was older than 75 years and two of them were older than 60 years; especially in patients with resistant hypertension, PHA screening regardless of age will be very meaningful in terms of regulating the treatment of patients and reducing the complications that may develop due to high blood pressure.

Study Limitations

The limitation of our study is the small number of study population because it is a single-center study.

Conclusion

In summary; primary hyperaldosteronism is one of the important causes of secondary hypertension and has a certain prevalence in hypertensive patients. Although there are various methods as screening tests, the most commonly used method is the aldosterone/renin ratio and it is a disease that is practical to screen. Considering the various cardiovascular diseases that PHA is associated with, and the simplicity of treatment of PHA, we strongly believe that the screening threshold for PHA should be kept as low as possible and should be independent of age.

Ethics Committee Approval: Ethics committee approval was obtained from Memorial Bahçelievler Hospital Local Ethic Committee (approval number: 20, date: 13.09.2021).

Informed Consent: Written consent was obtained from all the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - G.B., E.Ş.H., Y.E.U.; Concept - G.B., Y.E.U., E.Ş.H., L.B.A.; Design - G.B., L.B.A., E.Ş.H.; Data Collection or Processing - G.B., Ö.Ö.,; Analysis or Interpretation - L.B.A., Y.E.U., E.Ş.H., M.N.; Literature Search - G.B., Ö.Ö., E.Ö., L.B.A., M.N.; Writing - G.B., E.Ö., E.Ş.H.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P. Hyperaldosteronism among black and white subjects with resistant hypertension. Hypertension 2002; 40: 892-6.
2. Strauch B, Zelinka T, Hampf M, Bernhardt R, Widimsky J Jr. Prevalence of primary hyperaldosteronism in moderate to severe hypertension in the Central Europe region. J Hum Hypertens 2003; 17: 349-52.
3. Li YM, Ren Y, Chen T, Tian HM. Update and Research Progress in the Diagnosis of Primary Aldosteronism. Sichuan Da Xue Xue Bao Yi Xue Ban 2020; 51: 267-77.
4. Loh KC, Koay ES, Khaw MC, Emmanuel SC, Young WF Jr. Prevalence of primary aldosteronism among Asian hypertensive patients in Singapore. J Clin Endocrinol Metab 2000; 85: 2854-9.
5. Concistrè A, Petramala L, Bisogni V, Mezzadri M, Olmati F, Saracino V, et al. Subclinical atherosclerosis due to increase of plasma aldosterone concentrations in essential hypertensive individuals. J Hypertens 2019; 37: 2232-9.
6. Montori VM, Young WF Jr. Use of plasma aldosterone concentration-to-plasma renin activity ratio as a screening test for primary aldosteronism. A systematic review of the literature. Endocrinol Metab Clin North Am 2002; 31: 619-32.
7. Pratt RE, Flynns JA, Hobartn PM, Paul M, Dzau J. Different secretory pathways of renin from mouse cells transfected with the human renin gene. J Biol Chem 1988; 263: 3137-41.
8. Hundemer GL, Vaidya A. Primary Aldosteronism Diagnosis and Management: A Clinical Approach. Endocrinol Metab Clin North Am 2019; 48: 681-700.
9. Monticone S, Burrello J, Tizzani D, Bertello C, Viola A, Buffolo F, et al. Prevalence and clinical manifestations of primary aldosteronism encountered in primary care practice. J Am Coll Cardiol 2017; 69: 1811-20.
10. Murata M, Kitamura T, Tamada D, Mukai K, Kurebayashi S, Yamamoto T, et al. Plasma aldosterone level within the normal range is less associated with cardiovascular and cerebrovascular risk in primary aldosteronism. J Hypertens 2017; 35: 1079-85.
11. Catena C, Colussi G, Nadalini E, Chiuch A, Baroselli S, Lapenna R, et al. Cardiovascular outcomes in patients with primary aldosteronism after treatment. Arch Intern Med 2008; 168: 80-5.
12. Mosso L, Carvajal C, González A, Barraza A, Avila F, Montero J, et al. Primary aldosteronism and hypertensive disease. Hypertension 2003; 42: 161-5.
13. Baudrand R, Guarda FJ, Torrey J, Williams G, Vaidya A. Dietary sodium restriction increases the risk of misinterpreting mild cases of primary aldosteronism. J Clin Endocrinol Metab 2016; 101: 3989-96.
14. Mulatero P, Stowasser M, Loh KC, Fardella CE, Gordon RD, Mosso L, et al. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. J Clin Endocrinol Metab 2004; 89: 1045-50.
15. Käyser SC, Deinum J, de Grauw WJ, Schalk BW, Bor HJ, Lenders JW, et al. Prevalence of primary aldosteronism in primary care: a cross-sectional study. Br J Gen Pract 2018; 68: e114-22.
16. Markou A, Pappa T, Kaltsas G, Gouli A, Mitsakis K, Tsounas P, et al. Evidence of primary aldosteronism in a predominantly female cohort of normotensive individuals: a very high odds ratio for progression into arterial hypertension. J Clin Endocrinol Metab 2013; 98: 1409-16.
17. Baudrand R, Guarda FJ, Fardella C, Hundemer G, Brown J, Williams G, et al. Continuum of renin-independent aldosteronism in normotension. Hypertension 2017; 69: 950-6.