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Original Article

Evaluation of Patients Performed With Saline Infusion Test With a Pre-diagnosis of Primary Hyperaldosteronism

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ABSTRACT

Background Primary hyperaldosteronism (PHA) is a primarily treatable cause of arterial hypertension characterized by low plasma renin and high aldosterone levels. The prevalence of secondary hypertension as a common endocrine cause is 5-13%. The plasma aldosterone/renin ratio (ARR) is the best available method for PHA screening. One or more confirmatory tests may be required to confirm or exclude patients' diagnoses. One frequently used confirmatory test is the saline infusion test (SIT). We aimed to screen the patients who underwent SIT with the preliminary diagnosis of PHA and to compare the results of the patients diagnosed with essential hypertension (EH) and PHA.

Material and Methods Seventy-seven patients with a history of drug-resistant hypertension or unexplained spontaneous or diuretic-induced hypokalemia or adrenal incidentaloma, or a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years) and undergoing saline infusion testing were included in the study.

Results Twenty-six (33.8%) of the patients were male, and 51 (66.2%) were female. The mean age of the patients was 54.5±13.7 years. EH was present in 39 (50.6%) patients, and PHA was present in 38 (49.4%) patients. Patients with PHA and EH were compared. There was no significant difference between mean systolic blood pressure, diastolic blood pressure, potassium, and aldosterone renin ratio (ARR) in the two groups ($p>0.05$). Basal plasma aldosterone ($p<0.05$), SIT 0^{th}, and 4^{th}-hour plasma aldosterone levels ($p<0.01$) was significantly higher in PHA than in EH. Aldosterone synthesizing adenoma (ASA) and idiopathic hyperaldosteronism (IHA) were compared. There were no significant differences between basal plasma aldosterone, SIT 0^{th}, and 4^{th}-hour plasma aldosterone levels, ARR, and potassium values ($p>0.05$). The mean sodium value was significantly higher than the IHA ($p <0.05$).

Conclusions Our study determined that the saline infusion test could be used to confirm the diagnosis of primary hyperaldosteronism. Its use alone was not sufficient in the differential diagnosis of aldosterone-synthesizing adenoma and idiopathic hyperaldosteronism.

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Introduction

Primary hyperaldosteronism (PHA) is a primarily treatable cause of arterial hypertension characterized by low plasma renin and high aldosterone levels.[1] Its prevalence is 5-13% as a common endocrine cause of secondary hypertension.[2] The two most common causes of PHA are bilateral idiopathic hyperaldosteronism (or idiopathic hyperplasia IHA, 60%) and unilateral aldosterone-secreting adenomas (ASA 30-40%).[3] Compared with patients with essential hypertension (EH), patients with PHA have a higher risk of cardiovascular and kidney disease.[4] Therefore, early diagnosis and treatment are essential. Treating PHA with either mineralocorticoid antagonists or unilateral adrenalectomy lowers blood pressure while correcting hypokalemia.It also improves impaired cardiac and renal function.[5]

The plasma aldosterone/renin ratio (ARR) is the best available method for PHA screening. Some drugs (diuretics, beta-blockers, etc.) and conditions (hypokalaemia, sodium restriction) may affect the test. If initial results are inconclusive or difficult to interpret, or if PHA is strongly suspected clinically, the ARR should be repeated.[6] It is recommended that patients with positive ARR undergo one or more confirmatory tests to confirm or exclude their diagnosis definitively. However, no further confirmatory testing is required in patients with hypokalemia with suppressed renin and plasma aldosterone level (PAL) >20 ng/dL.[6]

Clinical practice guidelines of the Endocrine Society recommend the following as confirmatory tests: saline infusion test (SIT), fludrocortisone suppression test, captopril challenge test , and oral sodium loading test. According to the 2008 Endocrine Society clinical practice guidelines, if the PAL measured at the 4th hour after SIT is below 5 ng/dL, PHA is excluded. If the PAL is above 10 ng/dL, PHA should be considered. The diagnosis is uncertain if the PAL is between 5-10 ng/dL.[7] On the other hand, Giacchetti et al.[8] suggested that a PAL above 7 ng/dL after SIT was sufficient to confirm the diagnosis of PHA. We aimed to screen the patients who underwent SIT with a prediagnosis of PHA and compare the results of the patients diagnosed with essential hypertension and PHA.

Material and Methods

This study was carried out in Bursa Uludag University Faculty of Medicine. The Uludag University Medical Board approved the study protocol. Seventy-seven patients with a history of drug-resistant hypertension, unexplained spontaneous or diuretic-induced hypokalemia or adrenal incidentaloma, or a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years) and undergoing saline infusion testing were included in the study.Seventy-seven patients whose β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers were discontinued at least two weeks before the test, and diuretics were discontinued at least four weeks before the test were included in the study.

In the SIT protocol, 500 mL/h 0.9% NaCl infusion was given intravenously for 4 hours between 08:00 and noon after the patient lay on his back for at least 2 hours. Plasma aldosterone and plasma renin levels were measured at 0 and 4 hours of the test. If the PAL measured at the 4th hour of SIT was below 5 ng/dL, PHA was excluded. If PAL was above 10 ng/dL, PHA was considered. If the PAL was between 5-10 ng/dL, the diagnosis was made according to the patient's clinical condition, laboratory, need for antihypertensive medication, and imaging.[6]

Multislice contrast-enhanced computed tomography (CT) or magnetic resonance imaging was used as an imaging technique in patients with suspected PHA. ASA was considered in patients with a unilateral solitary adrenal macroadenoma, a normal-appearing contralateral adrenal gland, and a positive laboratory test. IHA was considered in patients with bilateral micronodular hyperplasia or laboratory-positive patients with normal adrenal glands on CT.

Results

A total of 77 patients were included in the study. Of the patients, 26 (33.8%) were male, and 51 (66.2%) were female. The mean age of the patients was 54.5±13.7 years. EH was present in 39 (50.6%) patients, and PHA was current in 38

(49.4%) patients. Patients with PHA and EH were compared. There was no significant difference between the mean systolic blood pressure, diastolic blood pressure, potassium, and ARR in the two groups. There was a significant difference in basal plasma aldosterone ($p<0.05$) and plasma aldosterone ($p<0.01$) levels measured at the 0th and 4th hours of SIT test. Plasma aldosterone and SIT results of PHA and EH patients were given in Table 1. While the etiology was ASA in 24 (63.2%) patients diagnosed with PHA, it was IHA in 14 (36.8%) patients. Six (25%) of the patients diagnosed with ASA were operated on. Spironolactone was given to 25 (65.7%) patients diagnosed with PHA.

Two groups of patients with ASA and IHA were compared. The mean potassium value was 3.9±0.5 mEq/L in the group with ASA and 4.1±0.3 mEq/L in the group with IHA, and no significant difference was found between the two groups. The mean sodium value was 140.6±2.1 mEq/L in the group with ASA and 138.9±1.7 mEq/L in the group with IHA; a statistically significant difference was found ($p <0.05$). The basal plasma aldosterone and SIT results of ASA and IHA patients were showed in Table 2.

Discussion

The prevalence of PHA as the most common endocrine cause of secondary hypertension is 5-13%.[2] In addition, patients with PHA have a higher risk of cardiovascular and kidney disease than patients with EH.[4] Therefore, early diagnosis and treatment are essential. SIT is a frequently used test to confirm the diagnosis. We aimed to screen the patients who underwent SIT with a prediagnosis of PHA and compare the results of the patients diagnosed with EH or PHA.

In our patients with PHA, PAL (44.0±43.9 pg/ml) was significantly higher than in patients with EH (30.5±35.7 pg/ml). Seventy-seven patients participated in the study, and PHA (50.6%) was detected in 1 of 2 patients. In the study of Rossi et al.[9], PHA was found in 120 (37.9%) of 317 patients who underwent SIT. There was no statistical difference between the two groups in ARR. Ahmet et al.[10] suggested that the false positive ARR rate is particularly high in the female population compared to the male population and that different normal ranges should be developed for each gender. Twenty-six of our patients (33.8%) were male, 51 (66.2%) one of them was female.

Table 1. Comparison of PHA and EH laboratory results.

	PHA	EH	p value
Aldosterone (pg/mL)	44.0±43.9	30.5±35.7	<0.05
ARR	111.9±93.6	121.6±138.8	NS
SIT 0th hour aldosterone (pg/mL)	31.2±34.3	10.2±6.5	<0.01
SIT 4th hour aldosterone (pg/mL)	25.1±36.0	3.8±2.0	<0.01

NS: not significant, ARR: aldosterone renin ratio, SIT: saline infusion test.

Table 2. Comparison of ASA and IHA laboratory results.

	PHA	EH	p value
Aldosterone (pg/mL)	52.1±53.2	30.0±12.4	NS
ARR	117.1±102.9	102.8±77.9	NS
SIT 0th hour aldosterone (pg/mL)	35.7±42.2	24.4±15.9	NS
SIT 4th hour aldosterone (pg/mL)	31.1±45.0	15.7±7.1	NS

NS: not significant, ARR: aldosterone renin ratio, SIT: saline infusion test.

Female patients were more than males may have affected the result.

Studies also advocate that when calculating the ARR, the renin value should be fixed at a minimum (0.2 ng/mL/h or 2 mIU/ for PRA), and it is important, especially inpatient subgroups such as the elderly.[11] The mean age of our patients was 54.5±13.7 years. In addition, since patients with a prediagnosis of PHA and an ARR ratio of >20 were evaluated in this study, there is no data for patients with ARR <20 and a direct diagnosis of EH. These factors may have caused the ARR rates to be similar.

In the study of Alam et al.[12], patients diagnosed with PHA had HT for an average of 10.5 (3.5-18) years. Our patients had HT for an average of 13.0±8.2 years before PHA diagnosis. This indicates a significant delay between the onset of PHA and its diagnosis.

When the patients diagnosed with PHA and EH were compared, no difference was found between SBP and DBP. We can explain this by the fact that the population in which we perform SIT generally has severe hypertension, and 87% of our patients use antihypertensive drugs.

Although it did not reach statistical significance when comparing ASA and IHA, the mean PAL was 52.1±53.2 pg/mL in patients with ASA, while it was 30.0±12.4 pg/mL in IHA and was higher. While ARR was 117.1±102.9 in ASA, it was 102.8±77.9 in IHA, and there was no statistical difference. In addition, although the PAL measured at the 4th hour of SIT did not reach statistical significance, it was 31.1±45 pg/mL in ASA and 15.7±7.1 pg/mL in IHA. In the multicenter study by Rossi et al.[9], it was concluded that SIT was safe and specific to exclude PHA, but it had no place to differentiate between ASA and IHA. Arteriovenous sampling (AVS) was performed in 7 of our patients to differentiate ASA and IHA, but it was not successful because the right renal vein could not be catheterized. Therefore, the distinction between ASA and IHA could be made according to severe hypertension, spontaneous hypokalemia, high aldosterone levels, age and CT results. This is the limitation of our study and may have affected the results of IHA and ASA. This creates difficulties distinguishing between ASA and IHA for countries where AVS is difficult to reach.

When the two groups with ASA and IHA were compared, there was no statistical difference in potassium values when the two groups with PHA and EH were compared. The sodium value of the patients with ASA (140.6±2.1 mEq/L) was higher in the group with IHA (138.9±1.7 mEq/L), and it was statistically significant. Hypokalemia has been accepted as one of the distinguishing signs in PHA diagnosis. However, it was observed that less than 37% of patients with PHA presented with hypokalemia.[13] 87% of our patients were taking antihypertensive drugs at the time of admission. This may also have affected the results.

The limitations of our study can be listed as the retrospective nature of our study, the small number of patients, and the failure of our center in AVS.

Conclusions

In our study, it was determined that the saline infusion test can be used to confirm the diagnosis of primary hyperaldosteronism. In the differential diagnosis of aldosterone-synthesizing adenoma and idiopathic hyperaldosteronism, its use alone was not sufficient.

Acknowledgment

This study has been presented in 18th Uludag Internal Medicine National Winter Congress, 7th Bursa Family Medicine Association National Congress, 12th Uludag Internal Medicine Nursing Congress, 3-6 March 2022, Bursa, Turkey.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: CA; Study Design: CA; Supervision: CE, OOG; Data Collection and/or Processing: GA; Statistical Analysis and/or Data Interpretation: SC, OOG; Literature Review: SC, OOG; Manuscript Preparation: CA, OOG; and Critical Review: EA, FMS; Other: EE, EH.

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