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Etiology in resistant hypertension

Yaşar Culha[1], Özkan Gülmez[2], Banu İşbilen Başok[3], Ferruh Kemal İşman[4], Aytekin Oğuz

[1]Division of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkiye
[2]Department of Internal Medicine, Yağlıdere State Hospital, Giresun, Turkiye
[3]Department of Medical Biochemistry, Health Sciences University İzmir Tepecik Training and Research Hospital, İzmir, Turkiye
[4]Department of Medical Biochemistry, Institute of Health Sciences, Istanbul Medeniyet University, İstanbul, Turkiye
[5]Department of Internal Medicine, Institute of Health Sciences, Istanbul Medeniyet University, İstanbul, Turkiye

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ABSTRACT

Aims: Resistant hypertension is defined as blood pressure that remains above goal despite the concurrent use of 3 antihypertensive agents of different classes. In resistant hypertensive patients, revealing the cause of secondary hypertension may allow drug or surgical treatment for the correction of hypertension. Resistant hypertensive patients, a significant portion of the hypertensive population, is estimated to occur. We aimed to investigate general characteristics and factors that make it difficult to control blood pressure in resistant hypertensive patients and to identify the incidence of secondary hypertension and secondary hypertension causes that play a role in the etiology of resistant hypertension.

Methods: In the study, Turkish Republic Ministry of Health, İstanbul Medeniyet University Göztepe Training and Research Hospital Internal Medicine, Diabetes and Obesity clinic for any reason the applicant and resistant hypertension detected a total of 80 patients (32 men, 48 women, mean age: 62±10) were enrolled consecutively. The treatment characteristics of patients, as well as demographic, anthropometric, and biochemical data, were evaluated, and the cause of secondary hypertension and etiology distribution were determined.

Results: In resistant hypertensive patients, the frequency of secondary hypertension was 60% (men 71%, women 52%). The most common causes of secondary hypertension are primary hyperaldosteronism (45%), obstructive sleep apnea syndrome (15%), and thyroid disorders (11%), respectively. 40% of the cases were diabetic, and 77.7% obese. Left ventricular hypertrophy and proteinuria were the most frequently detected target organ damage (96% and 37.5%, respectively). The average salt consumption of 10.75 grams/day was observed (males 12.2 g/day for females 9.7 g/day). There was analgesic use in 41% of cases, and in 3 cases, cola intake.

Conclusion: Secondary hypertension was found to be 60% common. Compared to other studies in the literature, primary hyperaldosteronism and pheochromocytoma were more common causes of secondary hypertension, and the obstructive sleep apnea syndrome was lower than expected. Hypercortisolism is not detected, which can be considered a surprising finding.

Keywords: Resistant hypertension, etiology, secondary hypertension, primary hyperaldosteronism

INTRODUCTION

Resistant hypertension is defined as the inability to reduce blood pressure to targeted levels despite lifestyle regulation and the use of at least three antihypertensive drugs (provided that one of them is a diuretic) in appropriate doses.[1,2] In addition, patients who are using four or more antihypertensive drugs and whose blood pressure goal may or may not be achieved are also classified as having resistant hypertension.[1] The prevalence of resistant hypertension in the general hypertensive population is not precisely known. Still, cross-sectional studies and hypertension outcome studies suggest that resistant hypertension is common.[3,4] The ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack) study gives us the most appropriate information. In the ALLHAT study, which included a wide range of ethnically diverse participants (>33,000 cases), the blood pressure of 34% of the participants could not be controlled with an average of two drug treatments during approximately five years of follow-up.[3,4] When the study was completed, 27% of participants were taking three or more medications. In total, 49% of participants in the ALLHAT study had their blood pressure controlled with one or two drugs, indicating that 50% had their blood pressure controlled with three or more medications.

Age is the most crucial factor impeding blood pressure control in resistant hypertensive patients.[1,5] As age increases, blood pressure control becomes more difficult.[1,5]

Corresponding Author: Yaşar CULHA, drjasar@hotmail.com

The second most important factor is left ventricular hypertrophy and weight (body mass index [BMI] >30 kg/m²).[1] Chronic kidney disease is the strongest indicator of treatment resistance, defined as creatinine level greater than 1.5 mg/dl. High basal blood pressure, high dietary salt intake, DM (diabetes mellitus), black race, female gender, and living in the Southeastern United States are among the factors that make blood pressure control difficult.[6,7] Excessive consumption of cola is also among the causes of hypertension.[6] In patients with resistant hypertension, the underlying cause may include inaccurate blood pressure measurement, white coat hypertension, treatment noncompliance, arteriosclerosis, lifestyle changes (excessive salt intake in the diet, obesity, alcohol, cigarettes, cola), drug-related causes (cocaine, licorice root, NSAIDs including selective cox-2 inhibitors, aspirin, paracetamol, oral contraceptives, corticosteroids, erythropoietin, sympathomimetics, cyclosporine-tacrolimus) and secondary causes of hypertension (obstructive sleep apnea syndrome, chronic kidney disease, renal artery stenosis, primary aldosteronism, diabetes, pheochromocytoma, Cushing syndrome, and aortic coarctation).[1,6,7] Also, Monogenic causes of hypertension in young adults should be considered as the underlying secondary cause.[8] These factors should be investigated.

It is recommended to investigate secondary hypertension, especially in cases with high blood pressure that started before the age of 20 or after the age of 50, a sudden and unexplained increase in blood pressure, subclinical severe organ damage detected at diagnosis, and resistant hypertension.[9] Approximately 5-10% of hypertensive patients have a secondary cause.[10,11] Although this rate is thought to be higher in resistant HT, the total prevalence is unknown because studies on this are limited.[1,7] In a recent study by Pedrosa et al.,[12] the frequency of secondary HT in resistant HT was 65.6%. This study aims to investigate the causes of secondary hypertension in resistant hypertension patients who apply to the outpatient clinic.

METHODS

In the study, a total of 80 patients with resistant hypertension who were admitted to the Internal Medicine, Diabetes, and Obesity Outpatient Clinics of the Ministry of Health Medeniyet University Göztepe Training and Research Hospital for any reason were prospectively routinely examined and examined, and further evaluations were made in terms of the etiology of resistant hypertension. The approval of 'The Ethic Committee of Scientific Researches of the İstanbul Medeniyet University Göztepe Training and Research Hospital (Date: 27.11.2011, Decision No: 28/A) and the informed written consent of the patients were obtained for the study. The principles of the Declaration of Helsinki were followed throughout the study.

Criteria for Inclusion in the Study

Those who were 18 years of age and over and, as in the definition of resistant hypertension, whose target blood pressure could not be reached despite using three different antihypertensive drugs (including one diuretic) or cases who are using four or more antihypertensive drugs and whose target blood pressure level is reached or not.[1,5,6,12] The target blood pressure value is 140/90 mmHg for the general hypertensive group and 130/80 mmHg for those with DM and chronic kidney disease. The guidelines emphasize the importance of detecting pseudo-resistance related to (1) BP measurement technique problems, (2) white coat hypertension, and (3) medication/lifestyle noncompliance. For example, the 2018 European guidelines for resistant HT require inadequate control of BP to be confirmed by ambulatory blood pressure measurements (ABPM) or home blood pressure measurements (HBPM) and adherence to therapy to be validated.[13]

Exclusion Criteria

Patients with pregnancy, acute illness, or unfavorable clinical conditions.

Study Design

Patients who applied to internal medicine outpatient clinics and met the study's inclusion criteria were randomly selected regardless of gender. Gender, age, height, weight, BMI, waist circumference, smoking, and alcohol use history of the patients recorded. The presence of comorbid diseases in the patients was recorded. Names, dosing, and the number of anti-hypertensive drugs they are taking were recorded. The biochemical and urine analyses recorded include fasting blood sugar, total cholesterol, triglyceride, HDL, LDL, urea, creatinine, sodium, potassium, HbA1c, complete urinalysis, TSH, free T4, morning serum cortisol, protein/creatinine ratio in spot urine, GFR (glomerular filtration rate), 24-hour urine sodium, plasma aldosterone level, plasma renin activity, metanephrine, and normetanephrine levels in the 24-hour urine. The use of drugs and other substances that may cause hypertension or disrupt its control were recorded.

The ankle-brachial index (ABI) has been used to detect peripheral artery disease (PAD). The ABI measurement was performed using a hand-inflatable sphygmomanometer and a hand-held, with the help of flow Doppler ultrasonography, tibialis anterior and tibialis posterior arteries; Systolic pressures of both brachial arteries were measured; lower extremity systolic pressures to the value with higher pressure in the upper extremities found by dividing.[14] The resulting ABI is normally between 1.0 and 1.3. An ABI of less than 0.90 is considered diagnostic of PAD. Mild disease correlates

with an ABI ranging from 0.70 to less than 0.90, whereas moderate disease correlates with an ABI ranging from 0.40 to less than 0.70, and severe disease is associated with an ABI of less than 0.40.[14]

To calculate the amount of salt consumed daily, the subjects were asked to collect their urine for 24 hours. The amount of sodium excreted in the urine was recorded in milliequivalents (mEq). Since 1 gram of salt contains 17 mEq of sodium, the total sodium excreted in the urine was divided by 17 to determine the amount of salt consumed in grams.

Anthropometric Measurements

Waist circumference, fasting, standing, and mid-expiration were measured from the middle of the lower rib border and the anterior superior spina iliaca, naked, with a constant tension tape measure, and the value recorded in centimeters was taken. BMI (kg/m2) was calculated by dividing body weight in kilograms by height in square meters. BP indirect method, using Erkameter 3000 branded standard mercury table top sphygmomanometer, the last two of 3 measurements taken at 2-minute intervals from both arms in an upright sitting position with back support, after the patient has been rested for 5 minutes, without caffeine or tobacco use in the last 1 hour, without being allowed to talk. It was recorded by taking the average. Blood pressure levels are categorized based on the ESH-ESC 2007 hypertension guideline.[2] The patients measured their blood pressure two times a day for at least five days using their own devices to evaluate the white coat effect. Measurements in the morning and evening should be done during the following hours, after resting in a sitting position for at least 5 minutes, and by paying attention to the standard precautions recommended for measurement. Hypertension is diagnosed if the average HBPM values are ≥135/85 mmHg.[15]

Lower extremity pressures were measured for aortic coarctation, and a difference of more than 20 mmHg between upper extremity and lower extremity BP was considered significant.

Laboratory Data

In Göztepe Training and Research Hospital Biochemistry Laboratory, biochemical and hormonal examination results were obtained from venous blood samples taken after a night fast of at least 12 hours, using enzymatic, calorimetric, and chemiluminescent immunoassay methods on the Abbott Aeroset Autoanalyzer and Immulite-1000 device. GFR was calculated with the Cockcroft-Gault formula.

Evaluation of Conditions Affecting Blood Pressure

Patients were questioned about using additional medications and substances that would negatively affect BP. The use of NSAID and non-NSAID analgesics >three doses per week[1], steroids (oral, parenteral or inhaler), OKS (oral contraceptive), amphetamine, cocaine, erythropoietin, cyclosporine, tacrolimus, TCA (tricyclic antidepressant), licorice, and cola (≥ one can per day)[6] usage was questioned.

OSAS Evaluation

According to the Epworth sleep scale, patients' answers to each question were given a score between 0 and 3, and the total score was recorded based on the answers to 8 questions in the scale. A score of 10 or more was considered a positive screening test for OSAS.[16]

Left ventricular hypertrophy (LVH)

In patients without echocardiography, electrocardiography was performed according to the Sokolof-Lyon Criteria. In the electrocardiogram,

i) The sum of the voltages of the S wave in V1 and the R wave in V5 or V6 in the horizontal plane is over 35 mm,

ii) R wave greater than 26 mm in V5 or V6, or

iii) An R wave greater than 14 mm in DI or 11 mm in aVL was compatible with LVH.

Proteinuria

Microalbumin in 24-hour urine above 30 mg/day was considered microalbuminuria, and above 300 mg/day was considered macroalbuminuria.

Thyroid Disorders

TSH levels between 4 and 10 IU/ml were considered subclinical hypothyroidism, levels above 10 IU/ml were considered overt hypothyroidism, and levels below 0.5 IU/ml were considered hyperthyroidism [17].

Primary Hyperaldosteronism

Blood samples for serum aldosterone and PRA were taken at least 2 hours after getting out of bed in the morning and during a 5-15 minute sitting period.[18] Aldosterone antagonist use, if any, was discontinued three weeks before the tests. The blood samples were centrifuged with an NF 2000 brand centrifuge device at 4000 rpm for 10 minutes and then stored in a deep freezer at -80 degrees. Serum aldosterone (SA) and PRA (plasma renin activity) were studied by the RIA (radioimmunoassay) method (kit manufacturer: Immunotech, Beckman Coulter Inc.), and serum aldosterone was determined as pg/ml and PRA as ng/ml/hour. SA was converted from pg/ml to ng/dl, and the SA/PRA ratio was calculated in SA ng/dl and PRA ng/ml/hour units. For primary hyperaldosteronism, patients with SA>20 ng/dl and SA/PRA>30 were considered to have a positive screening test.

Pheochromocytoma

Metanephrine and normetanephrine in 24-hour urine were measured by HPLC (High-performance liquid

chromatography) method and as mcg/day. Metanephrine >400 mcg/day and normetanephrine >900 mcg/day values were considered positive screening tests for pheochromocytoma.[19]

Cushing's Syndrome

Patients were screened with 8:00 a.m. cortisol. Morning cortisol >20 mcg/day was considered hypercortisolemia. In cases with morning cortisol >20 mcg/dl, the test was repeated a second time, and ACTH measurement was performed between 08:00 and 10:00 in the morning.

Renovascular Disease

Renal US and renal Doppler US imaging of the patients were performed by doctors from the Department of Radiology at Göztepe Training and Research Hospital, and in Doppler US, a renal/aortic flow ratio of 3.5 and peak systolic velocity greater than two m/sec is positive for renal artery stenosis. It was evaluated as a finding. The renal parenchymal disease was staged as grade 0-3 according to Renal US, and changes in size were recorded.[20] If renal Doppler US findings support renal artery stenosis or the suspicion is still high, further examination was performed with gadolinium MR angiography for a definitive diagnosis. >50% stenosis in renal arteries was considered significant.

Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows 13.0 program was used. Descriptive statistical methods (Mean, Standard Deviation, ratio, frequency) were applied. Pearson correlation analysis was used to correlate mean blood pressure and obesity. The chi-square test was used to compare categorical variables, and the independent sample t-test was used for continuous variables. The results were evaluated at the 95% confidence interval, and the significance level was $p<0.05$.

RESULTS

The study included 80 resistant hypertension patients (32 men, 48 women, mean age: 62±10 years). The cases' mean systolic, diastolic, and mean arterial blood pressures were 149±16 mmHg, 88±9 mmHg, and 108±10 mmHg, respectively. The most common comorbidities were DM and CAD (40% and 16.3%, respectively) (Table 1).

While the average BMI of the cases is 32.6 kg/m², 46.8% of men are overweight with a BMI of 25-29.9 kg/m², and the majority of women, 47.9%, are in the obesity stage 1 category with a BMI of 30-34.9 kg/m². In total, 87.6% of women are in the obese (BMI≥30 kg/m²) category. The obese case rate in men is 47.7%. While 44 (55%) of the cases were using three different anti-hypertensive drugs, 36 (45%) were using four or more anti-hypertensive drugs. The average number of medications used in all cases was 3.6.

Table 1. Distribution of demographic, medical history, and comorbidity characteristics of the cases

	n=80
Age, years±SD	62±10
Gender, male/female	32/48
Waist circumference (cm), mean±SD	106.3±10.3
BMI, kg/m², mean (min-max.)	32.6 (21.5-45)
Tobacco use, n (%)	
Smoker	12 (15)
Non-smoker	68 (75)
Alcohol use, n (%)	
Drinking	2 (2.5)
Not drinking	78 (97.5)
Comorbidities, n (%)	
Diabetes mellitus	32 (40)
Coronary artery disease	13 (16.25)
Hypothyroidism	10 (12.5)
Chronic kidney disease	8 (10)
Hearth failure	3 (3.75)
Chronic obstructive pulmonary disease	2 (2.5)
Arrhythmia	2 (2.5)
Hyperthyroidism	1 (1.25)

SD: Standard deviation, BMI: Body mass index, min: Minimum, max: Maximum

32 (40%) of the cases had stage 1, 25 (31%) had stage 2, and 5 (6%) had stage 3 arterial blood pressure values. However, arterial blood pressure was <140/90 mmHg in 18 (23%) cases (These patients meet the criteria for resistant hypertension as they are taking four or more antihypertensive medications). A white coat effect was detected in 14 (17%) cases when the average of home measurements (three measurements) was compared with office measurements.

While the average salt intake of all cases was found to be 10.75 g/day, the salt intake was 12.2 g/day in men and 9.7 g/day in women (Table 2).

Table 2. 24-hour urine sodium averages of the cases according to gender and the estimated daily salt intake calculated accordingly

	Gender	n	Mean	Standard deviation
24-hour urine sodium averages (mEq/day)	All cases	80	182.9	84.8
	Male	32	208.9	80.7
	Female	48	165.6	83.8
24-hour salt (NaCL) intake (g/day)	All cases	80	10.75	4.9
	Male	32	12.2	4.7
	Female	48	9.7	4.9

According to echocardiography or ECG findings, left ventricular hypertrophy (LVH) was detected in 30 (37.5%) cases. LVH was detected in 18 (37.5%) women and 12 (37.5%) men, and the proportions are equal ($p=0.98$). PAH (peripheral artery disease) was detected in 24% of the cases. While microalbuminuria (30-300 mg/day) was detected in 77% of the cases, macroalbuminuria (≥300 mg/day) was detected in 19% of the cases, normoalbuminuria was detected in only 4% of the cases.

Stage-4 chronic kidney disease (GFR<30 ml/min) was detected in 4 (5%) of the cases. The sleep characteristics of the cases in terms of obstructive sleep apnea syndrome (OSAS) are given in Table 3. Accordingly, a positive screening test for OSAS was detected in 12 (15%) cases. Witnessed apnea was present in 10 (12.5%) of the cases.

Table 3. Epworth sleep scale evaluation of the cases, distribution of witnessed apnea and snoring.

	n=80
Epworth sleep scale positivity*, n (%)	12 (15)
Witnessed apnea, n (%)	10 (12.5)
Snoring, n (%)	61 (76.2)

*: Cases scoring ≥10 points according to the Epworth sleep scale are considered to have a positive screening for OSAS.

According to TSH values in terms of thyroid functions cases, 6 (7%) had subclinical hypothyroidism, 3 (4%) had hyperthyroidism; Thyroid functions were found to be expected (euthyroid) in the remaining 71 (89%) cases. Overt hypothyroidism was not detected in any cases. Further examination was performed with gadolinium MR angiography for renal artery stenosis (RAS) in 10 cases. Renal artery stenosis (stenosis >50% was taken as renal artery stenosis) was detected in 4 of these 10 cases (5% of all cases). Stenosis was 90% in one of these cases, 70% in two, and 60% in one. According to renal ultrasonography, grade 1 renal parenchymal disease was detected in 7 (8.75%) cases, grade 2 renal parenchymal disease was detected in 1 case, and there was no renal parenchymal disease in the remaining 72 cases. According to the morning serum cortisol measurements of the cases, hypercortisolemia (cortisol >20 mcg/dl) was detected in 4 (5%) of the cases in the 1st measurement. However, these cases' second cortisol measurements were within normal limits. In addition, the morning ACTH measurements of the cases with high initial measurements were also found to be within normal limits (0-100 pg/ml).

Primary hyperaldosteronism was detected in 36 (45%) of the cases. Secondary hypertension was present in 48 (60%) of all cases. While secondary hypertension was present in 23 (71%) of men, It was present in 25 (52%) of women (Table 4).

Table 4. Distribution of the presence of secondary HT in cases according to gender

	Secondary HT (present)	Secondary HT (absent)	Total
Male	23 (71%)	9 (29%)	32 (100%)
Female	25 (52%)	23 (48%)	48 (100%)
Total	48 (60%)	32 (40%)	80 (100%)

The most common causes of secondary hypertension in the cases were found to be primary hyperaldosteronism (45%), OSAS (15%), and thyroid disorders (11%), respectively (Figure). Renal parenchymal disease, renal artery stenosis, and pheochromocytoma were detected at equal rates of 5%.

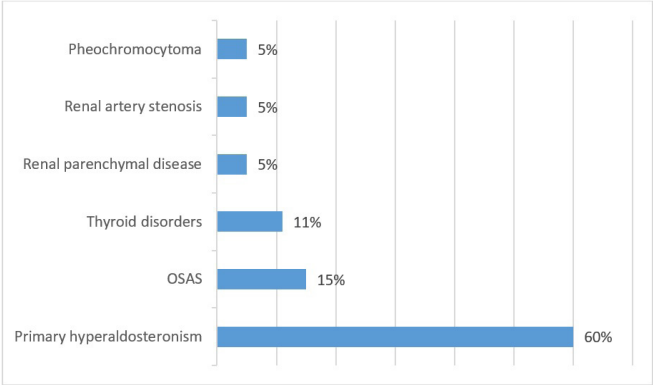

Figure 1. The frequency of causes for secondary hypertension

71 of 80 cases were using any type of diuretic (HCTZ, Indapamide, furosemide). Fifty-nine patients were using CCB (dihydropyridine+non-dihydropyridine), 55 patients were using ARB, 46 patients were using BB, 31 patients were using ACE inhibitors, 20 patients were using alpha-blockers, and two patients were using antihypertensive drugs from the other group. 55 of 71 cases using diuretics were using HCTZ. 26 of the cases use NSAID group analgesics and 7 of them use non-NSAID group analgesics. A total of 33 (41%) patients used analgesics. TCA (tricyclic antidepressant) was used in 5 cases, steroids in 3 instances, cola in 3 cases, OKS/HRT (oral contraceptive/hormone replacement therapy) in 2 cases, and erythropoietin in 1 case.

A weakly significant positive correlation was detected between BMI and MAP (mean arterial blood pressure) (r=0.237 p=0.034). In other words, as BMI increases, MAP also increases.

DISCUSSION

In our study, the frequency of secondary HT was found to be 60%. The frequency of secondary hypertension was found to be higher in men than in women. The frequency of secondary hypertension in the general hypertensive population is approximately 10%, but data on its frequency in the resistant hypertensive population are limited.[13] In a study by Pedrosa et al.,[12] the frequency of secondary HT in resistant HT was 65.6%. In our study, primary hyperaldosteronism (PHA) appears to be the most common cause of secondary hypertension. PHA was detected in 36 (45%) of the cases, and this rate is higher than in previous studies. Namely, in studies where SA/PRA was used as a screening test, PHA was found to be between 5-15% in the general hypertensive population,[21,22] and in recent years, there

are studies in which PHA was found to be between 20-30% in the resistant hypertensive population.[1,7] Common causes of secondary hypertension are OSAS, renal artery stenosis, chronic kidney disease, and PHA. More rare causes are pheochromocytomas, Cushing's syndrome, hyperparathyroidism, thyroid disorders, and aortic coarctation.[1,7,23] In many sources, the most common causes of secondary hypertension, especially in older ages, are shown to be renovascular and renal parenchymal diseases.[10,11] The frequency of renovascular HT in the hypertensive population over the age of 65 was found to be 7%; it is thought to be more common in resistant hypertensives.[12,24] Renal parenchymal disease in resistant hypertension: It is stated that it is seen at a rate of 2-5%.[12,24,25] OSAS has been identified as the most common cause of secondary HT in resistant HT (between 60% and 83%), with PHA accounting for 5-10%.[12,26]

It is known that beta-blocker group drugs may increase false positivity because they may reduce renin levels.[27,28] For this reason, it is recommended that this group of medications be discontinued two weeks before screening for PHA. However, this was not possible in a quarter of our patient group due to cardiac problems. It has also been reported that ACEIs, ARBs, diuretics, and dihydropyridine group CCBs may reduce the SA/PRA ratio and cause false negatives.[18,28] However, the fact that our cases already had resistant hypertension, a significant portion of them had stage-2 and 3 BP values, and that many cases were already using anti-hypertensive drugs from 4 or more groups (36 cases used ≥4 drugs) prevented these drugs from being discontinued. In our study, the diagnosis of cases with positive screening for PHA should be confirmed with salt suppression tests and radiological evaluations (computed tomography and/or magnetic resonance imaging). Due to cost, these additional examinations could not be performed within the scope of the study, but cases with positive screening tests were referred for further examination.

In recent years, studies have reported obstructive sleep apnea syndrome (OSAS) as the most common cause of secondary hypertension in resistant hypertensive patients.[12] Different studies have reported that the prevalence of OSAS in resistant hypertension varies between 60% and 83%.[12,26] We could not perform polysomnography to diagnose OSAS in our cases, but we scored according to the Epworth sleep scale, which is considered a screening test and shows daytime sleepiness. Accordingly, only 12 (15%) of the cases had a positive screening test according to the Epworth sleep scale. Thus, contrary to studies in recent years, a meager rate of positive screening for OSAS was detected in our cases. However, in studies where OSAS rates were high, polysomnography, the gold standard for diagnosis, was used.

Hypothyroidism is more common as a cause of secondary hypertension, especially in the 60s [10]. Approximately 3-5% of all patients with hypertension have hypothyroidism, but data on resistant hypertension are limited.[29] In a few studies, thyroid disease has been reported as a secondary cause of HT at a rate of 1-2%.[23] Thyroid disorder was detected in 11% of our cases, and this rate can be considered to be higher than expected. Hypothyroidism alone was detected in 7%.

Increased extracellular fluid load makes controlling blood pressure difficult in chronic kidney disease. This effect is more pronounced when GFR falls below 30 ml/min, which occurs in stage-4 kidney disease.[23,24] It is stated in the literature that renal parenchymal disease (GFR is taken as <30 ml/min) is seen at a rate of 2-5% in resistant hypertension.[23-25] In our study, renal parenchymal disease was detected at a rate of 5%, similar to the literature.

It is stated that the incidence of renal artery stenosis increases, especially in hypertensive patients aged 65 and over.[10] While the rate of renovascular hypertension was below 1% in unselected patient groups, this rate was reported to be 10% in the hypertension patient group examined for diagnostic evaluation [31]. There are also studies indicating that it is detected in 2-5% of resistant hypertensive patients.[12] In our study, renal artery stenosis was detected in 4 (5%) cases, similar to the stated rates.

Pheochromocytoma, another cause of secondary hypertension, was detected in 4 (5%) patients. The frequency of pheochromocytoma in the general hypertensive population is between 0.1-0.6%.[32] Although its frequency in the resistant hypertensive population is unknown, publications in the form of case reports have increased in recent years. The rate found in our study appears to be higher than expected. Due to cost, radiological imaging (computed tomography and/or magnetic resonance imaging) could not be performed for pheochromocytoma within the scope of the study. Still, cases with positive screening tests were referred for further examination.

Although morning cortisol is not recommended for screening patients for Cushing's syndrome, it is widely used in outpatient clinic settings because it is easily applicable. It is more appropriate to repeat at least 2-3 measurements instead of a single measurement. The annual incidence of Cushing syndrome in the general population is 2 per million. It is detected at rates close to 2% in the screening of high-risk populations with obesity or adrenal incidentaloma.[33] Its frequency in resistant hypertension is unknown. Although most of our cases were obese, hypercortisolism was not detected in any of our cases. However, it may be more appropriate to screen these cases for Cushing's syndrome with further tests.

In the HYDRA (Hypertension and Diabetes Risk Screening and Awareness) study, which included 45125 primary care patients, a significant increase in the prevalence of hypertension was found as BMI increased.[34] In the same study, it was observed that as BMI increased, BP control became more complex, and there was a significant increase in the number of antihypertensive medications used. Similarly, in our study, 87.4% of the cases were obese, and it was determined that as BMI increased, mean arterial pressure (MAP) increased in direct proportion (r: 0.237 p: 0.034). Similar to other studies, this supports the idea that obesity is an essential factor that disrupts BP control in our cases.

Type 2 DM and HT are standard in all societies and often coexist. It is estimated that approximately 50-70 million individuals in the USA have HT with insulin resistance.[27] In two separate studies conducted on resistant hypertensive patients, the coexistence of DM and HT was found to be 30% and 35%.[23,35] 40% of the cases in our study had DM, which is slightly above the stated rates. DM was found to be the most common comorbid condition in our cases.

The recommended adequate daily sodium intake corresponds to 3.8 g of sodium chloride per day, which may be difficult to achieve today.[36] The achievable target is less than 5 g per day (85 mEq/day) of sodium chloride.[36,37] It has been determined that daily salt consumption in Turkish society is approximately 18 g (SALTÜRK-2008). In the same study, daily salt consumption was 19.3 g in men and 16.8 g in women. The average salt consumption of the cases in our study corresponds to 10.75 g/day sodium chloride. Men's daily salt intake was higher than women's (12.2 grams versus 9.7 grams). This shows that salt intake was significantly above the recommended daily salt consumption in our cases and may have a severe role in the emergence of resistance to treatment.

In our study, NSAID and non-NSAID analgesic use was determined in the majority of the cases. Meta-analyses indicate that analgesic use increases mean arterial pressure by approximately five mmHg.[1] Tricyclic antidepressant use in 5 cases, steroid use in 3 cases, oral contraceptive use in 2 cases, and erythropoietin use in 1 case were detected as other drug uses that disrupted BP control. In 3 cases, ≥ one can of cola was consumed daily. The study conducted by Winkelmayer et al.[6] showed that drinking ≥1 can of cola per day, regardless of whether it is sugary or diet cola, increases BP statistically significantly. This shows that cola intake may harm BP control in our 3 cases.

Left ventricular hypertrophy (LVH) and proteinuria are essential factors that make BP control difficult in resistant hypertension.[1,38] In our study, proteinuria was detected in 96% of our cases, and LVH was detected in 37.5%. In resistant HT studies, proteinuria is 30-35%, and LVH is detected at 20%.[25] Proteinuria and CVH are indicators of target organ damage seen at higher-than-expected rates in our study.

CONCLUSION

As a result, the frequency of secondary HT was found to be 60%, which is higher than expected. The frequency of primary hyperaldosteronism and pheochromocytoma as secondary causes of HT was higher than other studies in the literature. In contrast, obstructive sleep apnea syndrome was lower than expected. The fact that hypercortisolism was never detected can be considered a surprising finding. It has been observed that the presence of obesity and diabetes and excessive dietary salt consumption are the most critical factors that make blood pressure control difficult in patients with resistant hypertension.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Istanbul Medeniyet University Göztepe Training and Research Hospital Clinical Researches Ethics Committee (Date: 27.11.2011, Decision No: 28/A)

Informed Consent

Written consent was obtained from the patient participating in this study.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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REFERENCES

1. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment. *Hypertension.* 2008;51(6): 1403-1419.

2. Mansia G, De Backer G, Dominiczak A, et al. 2007 ESH-ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Blood Press* 2007;16(3):135-232.
3. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angio-tensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288(23):2981-2997.
4. Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings: the Antihypertensive and Lipid-Lowering and Treatment to Prevent Heart Attack Trial (ALLHAT). *J Clin Hypertens*. 2002;4(6):393-404.
5. Lloyd-Jones DM, Evans JC, Larson MG, O'Donnell CJ, Rocella EJ, Levy D. Differential control of systolic and diastolic blood pressure: factors associated with lack of blood pressure control in the community. *Hypertension*. 2000;36(4):594-599.
6. Winkelmayer WC, Stampfer MJ, Willett WC, Curhan GC. Habitual caffeine intake and the risk of hypertension in women. *JAMA*. 2005;294(18):2330-2335.
7. Pimenta E, Gaddam KK, Oparil S. Mechanisms and treatment of resistant hypertension. *J Clin Hypertension*. 2008;10(3):239-244.
8. Gök F, Demir ME. Diagnosis and treatment of monogenic hypertension in children: monogenic hypertension. *J Eur Intern Med Professionals.* 2024;2(1):31-39.
9. Carey RM, Calhoun DA, Bakris GL,et al. American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. *Hypertension*. 2018;72(5):e53-e90.
10. Viera AJ. Resistant hypertension. *J Am Board Fam Med*. 2012; 25(4):487-495.
11. Omura M, Saito J, Yamaguchi K, Kakuta Y, Nishikawa T. Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. *Hypertens Res*. 2004;27(3):193-202.
12. Pedrosa RP, Drager LF, Gonzaga CC, et al. Obstructive sleep apnea: the most common secondary cause of hypertension with resistant hypertension. *Hypertension.* 2011;58(5):811-817.
13. Lamirault G, Artifoni M, Daniel M, Barber-Chamoux N, Nantes University Hospital Working Group On Hypertension. Resistant hypertension: novel insights. *Curr Hypertens Rev*. 2020;16(1):61-72.
14. Mohler ER III. Peripheral arterial disease: identification and implications. *Arch Intern Med*. 2003;163(19):2306-2314.
15. Chobanian AV, Bakris GL, Black HR, et al. the seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA*. 2003; 289(19):2560-2572.
16. Harding SM. Prediction formulae for sleep-disordered breathing. *Curr Opin Pulm Med*. 2001;7(6):381-385.
17. Türkiye Endokrinoloji ve Metabolizma Derneği, Tiroid Çalışma Grubu. Tiroid Hastalıkları Tanı ve Tedavi Kılavuzu 2020. Türkiye Klinikleri: 2020. Available from: https://file.temd.org.tr/Uploads/publications/guides/documents/20200929134733-2020tbl_kilavuzf527c34496.pdf?a=1
18. Funder JW, Carey RM, Fardella C, et al. Case detection, diagnosis and treatment of patient with primary aldosteronism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2008;93(9):3266-3281.
19. Sawka AM, Jaeschke R, Singh RJ, Young WF Jr. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. *J Clin Endocrinol Metab*. 2003;88(2):553-558.
20. Shivashankara VU, Shivalli S, Pai BH, et al. A comparative study of sonographic grading of renal parenchymal changes and estimated glomerular filtration rate (eGFR) using modified diet in renal disease formula. *J Clin Diagn Res*. 2016;10(2):TC09-TC11.
21. Seiler L, Rump LC, Schulte-Mönting J, et al. Diagnosis of primary aldosteronism: value of different screening parameters and influence of antihypertensive medication. *Eur J Endocrinol*. 2004;150(3):329-337.
22. Morillas P, Castillo J, Quiles J, et al. Prevalence of primary aldosteronism in hypertensive patients and its effect on the heart. *Rev Esp Cardiol.* 2008;61(4):418-421.
23. Kumar N, Calhoun DA, Dudenbostel T. Management of patients with resistant hypertension: current treatment options. *Integr Blood Press Control*. 2013;6:139-151.
24. Textor SC, Lerman L. Renovascular hypertension and ischemic nephropathy. *Am J Hypertens*. 2010;23(11):1159-1169.
25. Renovascular Hypertension. In: Kaplan NM, Lieberman E, Neal WA. Kaplan's Clinical Hypertension. 8th ed. Lippincott Williams & Wilkins: 2002:381-403.
26. Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *J Hypertens*. 2001;19(12):2271-2277.
27. Force AHT. AACE Guidelines. *Endocr Pract.* 2006;12(2):193.
28. Mulatero P, Rabbia F, Milan A, et al. Drug effects on aldosterone/plasma renin activity ratio in primary aldosteronism. *Hypertension*. 2002;40(6):897-902.
29. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med*. 2001;344(7):501-509.
30. Khawaja Z, Wilcox CS. Role of the kidney in resistant hypertension. *Int J Hypertens*. 2011;2011:143471.
31. Renovascular Hypertension. In: Massry SG, Glassock RJ, eds. Massry's and Glassock's Textbook of Nephrology. Williams&Wilkins: 2001:1159-1168.
32. Ganguly A, Grim CE, Weinberger MH, Henry DP. Rapid cyclic fluctuations of blood pressure are associated with an adrenal pheochromocytoma. *Hypertension*. 1984;6(2 Pt 1):281-284.
33. Lindholm J, Juul S, Jorgensen JO, et al. Incidence and late prognosis of Cushing's syndrome: a population-based study. *J Clin End Metab*. 2001;86(1):117-123.
34. Bramlage P, Pittrow D, Wittchen HU, et al HYDRA (Hypertension and Diabetes Risk Screening and Awareness) AJH. 2004; 17: 904-910.
35. de la Sierra A, Segura J, Banegas JR, et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ABPM. *Hypertension*. 2011;57(5):898-902.
36. Cutler JA, Follman D, Alexander PS. Randomized controlled trials of sodium reduction: an overview. *Am J Clin Nutr*. 1997; 65(Suppl 2):643-651.
37. Otten J, Pitzi Helliwig J, Meyers LD. The dietary reference intakes: the essential guide to nutrient requirements. National Academies Press: 2006.
38. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*. 2003;42(6):1206-1252.