Approach to cases with resistant hypertension

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Abstract

Resistant hypertension is defined as blood pressure that remains above 140/90 mm Hg despite the concurrent use of optimal dose of 3 antihypertensive agents of different classes. Ideally, 1 of these 3 agents should be a diuretic agent. The etiology of resistance hypertension is multifactorial. Successful treatment requires identification and reversal of lifestyle factors (obesity, dietary salt intake, alcohol intake, lack of adherence to prescribed medicines, and interfering substances), and to exclude the presence of pseudoresistance. Once confounding factors have been ruled out, evaluation for potentially treatable secondary causes of hypertension should be considered. Most forms of secondary hypertension are related with adrenal or renal disorders such as primary hyperaldosteronism and renovascular disease. Although, obstructive sleep apnea syndrome is not a typical cause of secondary hypertension, it is commonly present in resistant hypertension. Diagnostic workup and management of resistant hypertension were discussed in different clinical presentations. *(Anadolu Kardiyol Derg 2014; 14: 192-5)*

Key words: resistant hypertension, secondary hypertension, renovascular disease, primary hyperaldosteronism, obstructive sleep apnea syndrome

Introduction

Resistant hypertension is defined as blood pressure that remains above 140/90 mm Hg despite the concurrent use optimal doses of 3 antihypertensive agents of different classes, one being a diuretic. The spectrum of resistant hypertension also includes patients whose blood pressure can be controlled by four or more medications. The exact prevalence of resistant hypertension is unknown but the reported prevalence is 10-15% at reference clinics.

The accurate diagnosis and appropriate evaluation of resistant hypertension require exclusion of pseudoresistance, identification of important contributing factors (such as diet and antihypertensive drug compliance, and interfering substances) and diagnosis of underlying secondary causes of hypertension. The most common causes of pseudoresistance are white-coat hypertension and poor medicine adherence. Common factors contributing to development of resistance to antihypertensive treatment include high dietary salt intake, use of medications that can interfere with pharmacologic treatment, especially nonsteroidal anti-inflammatory agents, and lifestyle factors such as weight gain and lack of physical exercise. The likelihood of a secondary cause of hypertension is increased in patients with resistant hypertension. Renal parancymal disorders, renovascular diseases and primary hyperaldosteronism are the most common secondary causes of resistant hypertension, obstructive sleep apnea syndrome (OSAS) should be particularly evaluated in patients who are obese (1-3).

The purpose of this review is to discuss the diagnostic workup and management of resistant hypertension in patients with different clinical presentations.

Case 1

A 64-year-old man with a past history of essential hypertension that was once controlled with amlodipine monotherapy, presented with uncontrolled blood pressure despite taking multiple antihypertensive regimens (amlodipine 10 mg/day, carvedilol 25 mg/day, lisinopril 10/ hydrochlorothiazide 12.5 mg/day) for 1 month. For the preceding 10 days he also began to have nausea, vomiting, and fatigue. His family history was remarkable for coronary artery disease and essential hypertension in his brother.

Findings on physical examination were as follows; blood pressure 190/110 mm Hg in both arms, pulse rate 96 beats/min and regular, and body mass index 27 kg/m^2. He was dyspneic and orthopneic, bilateral inspiratory rales were heard in lungs on auscultation, and +2 bilateral pitting edema on both legs was

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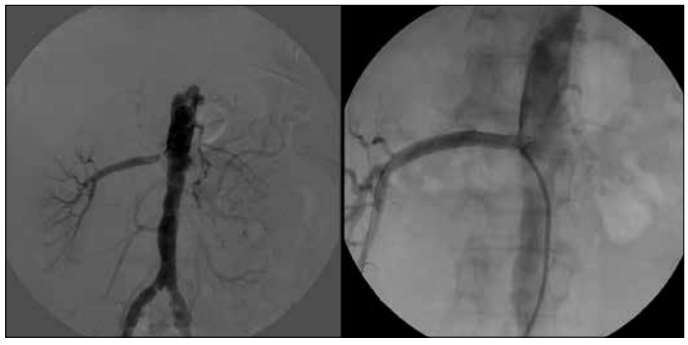

Figure 1. Right proximal renal artery stenosis secondary to atherosclerosis. Before (A) and after (B) successful percutaneous angioplasty

noted. He gave up smoking 10 years ago. He has no history of alcohol or any agents interfering with blood pressure control.

Serum tests follows: hemoglobin: 10.3 g/L, blood urea nitrogen (BUN) 124 mg/dL, serum creatinine 14.4 mg/dL, sodium 136 mEq/L, potassium 6.0 mg/dL, calcium 7.9 mg/dL and phosphorus 13 mg/dL. The patient's glomerular filtration rate was 4 ml/min according to MDRD formula, and urinary protein to creatinine ratio was 1.1. Arterial blood gas analysis showed a pH 7.24 and HCO3 18 mmol/L.

Electrocardiography revealed sinus rhythm with left ventricular hypertrophy. Left ventricular hypertrophy, ¼ mitral and tricuspid regurgitation, and normal systolic function (EF >%60) were present at echocardiography. Grade II hypertensive retinopathy was detected on fundus examination. Chest radiography demonstrates bat wing alveolar edema with a central distribution and sparing of the lung cortex.

The patient was hospitalized at intensive care unit because of high blood pressure complicated by target organ damage (hypertensive emergency; including acute kidney injury, and pulmonary edema). An intravenous antihypertensive regimen (nitroglycerin, furosemide) and hemodialysis therapy were initiated. After 4 liter of fluid removal from the body by ultrafitration on two hemodialysis seasons, the patient's blood pressure was decreased to about 150/100 mm Hg.

Renal ultrasonography revealed discrepancy between sizes of both kidneys with the left kidney being smaller. Digital subtraction angiography (DSA) was performed because of a high suspicion of renal artery stenosis. DSA showed complete occlusion of the left renal artery and 95% stenotic right renal artery. After bilateral percutaneous transluminal angioplasty of the renal arteries (PTRA), stenotic right renal artery was revascularized but it was not possible to vascularize left renal artery (Fig. 1A, B). Three days after the PTRA, renal function improved and blood pressure gradually decreased and thus antihypertensive drug requirement was reduced. His blood pressure was controlled with amlodipine monotherapy. The patient was discharged with a BUN 46 mg/dL, a creatinine 2.3 mg/dL, and a blood pressure of 130/80 mm Hg.

One year after the PTRA his mean blood pressure was below 140/90 mm Hg with amlodipine 10 mg/day while serum BUN and creatinine levels were 32 mg/dL and creatinine 1.5 mg/dL respectively. In addition, right renal artery was patent on duplex ultrasonography.

Case 2

A 38-year-old woman presented with the complaints of weakness, fatigue, and uncontrolled hypertension. The patient had had hypertension for 3 years, and had been taking 10 mg amlodipine and 160 mg valsartan for control of blood pressure. Fifteen days ago valsartan dose was increased to 320 mg and 25 mg hydrochlorothiazide was added on her current antihypertensive medications because of uncontrolled blood pressure. She had no history of smoking, alcohol intake, or use of any medications known to increase blood pressure. She had lost 10 kg weight in last four years.

On physical examination, the patient's blood pressure was 160/85 mm Hg on right arm and 170/90 mm Hg on left arm, and her pulse rate was 82 beats/min, and body mass index was 35 kg/m^2.

On laboratory examination serum potassium level was below the normal limit on two different samples (K: 3.1-3.3 mg/dL). Complete blood count, creatinine, sodium, calcium, liver functions tests, fasting glucose and lipid profiles, thyroid function test, glomerular filtration rate, and urinary albumin excretion were within normal limits.

Electrocardiography showed normal sinus rhythm. Systolic function was normal on echocardiography and so was the fundus examination.

Despite addition of metoplolol 100 mg/day and discontinuation of hydrochlorothiazide because of hypokalemia, blood pressure remained uncontrolled (office blood pressure was 160/100 mm Hg and home blood pressure reading were 155-150/80-85 mm Hg). As the patient had resistant hypertension combined with hypokalemia, she was evaluated for secondary hypertension including endocrine and renal causes. Renal ultrasonography and duplex ultrasonography ruled out of renovascular and renal parancimal pathology. Plasma TSH, free metanephine, normetanephrine, fasting cortisol levels, and 24-hour urinary free cortisol level were within normal limits. Plasma aldosterone concentration (PAC) was 32 ng/dL (>15 ng/mL), plasma renin activity (PRA) was 0.8 ng/mL/h (<1 ng/ml/h), and PAC/PRA ratio was 40 (>20). Sodium loading test with measurement of 24 hour urine aldosterone excretion was done to confirm the diagnosis of primary hyperaldosteronism. The diagnosis of primary hyperaldoteronism was confirmed by a high 24 hour urine aldosterone level. No adrenal mass was found by computed tomography of adrenal glands. Because of a high possibility of bilateral idiopathic hyperplasia due to hyporeninemic hyperaldosteronism we started 100 mg spiranolactone therapy in addition to current optimal doses of 3 antihypertensive drugs (valsartan 320 mg/day, amlodipine 10 mg/day, and metoprolol 100 mg/day). One month after of spironolactone therapy blood pressure gradually decreased and metoprolol and amlodipine were withheld. Her blood pressure came under control (<140/90 mm Hg) with half dose valsartan 160 mg/day and spiranolactone 100 mg/day on the second month of spiranolactone therapy.

Case 3

A 62-year-old man with history of hypertension and dyslipidemia, was referred to our department for uncontrolled blood pressure. The patient had a history of HT that was once con-

trolled with losartan 100 mg/day, amlodipine 10 mg/day, and carvedilol 12.5 mg/day since 10 days. Three days ago he had admitted to emergency room with chest pain related to high blood pressure (190/110 mm Hg). The cardiologist ruled out an acute coronary syndrome. Later the day his blood pressure decreased to 160/90 mm Hg by administration 25 mg sublingual captopril. The patient was discharged from emergency room with losartan 100/hydrochlorothiazide 12.5 mg/day.

He had not smoked cigarettes for 5 years. He usually takes non-steroidal anti-inflammatory drugs for headache.

On his physical examination blood pressure readings in right and left arms were 160/100 mm Hg and 150/90 mm Hg, respectively: body mass index was 32.2 kg/m^2. Other systemic examination was unremarkable.

Complete blood count, creatinine, electrolytes, liver function tests, glucose and thyroid function tests were all within normal limits. Lipid profile (total cholesterol: 250 mg/dL, low density lipoprotein cholesterol: 155 mg/dL, triglyceride: 200 mg/dL) and urinary albumin extraction (microalbuminuria 110 mg/day) were slightly elevated.

Electrocardiography revealed sinus rhythm. Echocardiography revealed left ventricular concentric hypertrophy, right atrial enlargement, and normal systolic function (EF >67%). Grade I hypertensive retinopathy was detected on fundus examination. No abdominal pathology was found on abdominal ultrasonography.

His blood pressure was still uncontrolled with optimal doses of 4 antihypertensive agents one of which was diuretic, and life still changes (low sodium consumption, regular exercise, and 8 kg weight loss) in last 2 months. His office blood pressure was 180/110 mm Hg and mean daytime blood pressure was 162/98 mm Hg, and mean nocturnal blood pressure was 158/90 mm Hg, consistent with a non-dipper pattern. Doxazosin 4 mg/day was added to his previous drug regimen.

There were no signs of secondary causes of hypertension such as renovascular disease, primary aldosteronism, Cushing syndrome, pheochromocyctoma, and thyroid diseases.

A polysomnography (PSG) was performed to rule out OSAS owing to presence of morning asthenia with headache, dryness in the mouth and pharynx, and snoring. PSG revealed an apnea-hypopnea index of 25/hour, which was consistent with moderate OSAS. Continuous positive airway pressure (CPAP) therapy was initiated with pressure of 8 cm H_20 for 5 hours. One month later, blood pressure showed gradual decrease with concomitant improvement of symptoms. On ambulatory blood pressure monitoring (ABPM) new mean daytime blood pressure was 138/85 mm Hg and mean nocturnal blood pressure was 122/74 mm Hg with a dipper pattern, and hence amlodipine, doxazosin and carvedilol were discontinued.

Blood pressure remained within normal limits (<140/90 mm Hg) at home and office controls with losartan 100 mg and 12.5 mg hydrochlorothiazide.

Discussion

Resistant hypertension is defined as blood pressure that remains above 140/90 mm Hg despite the concurrent use of 3 antihypertensive agents of different classes at optimal doses. Ideally, 1 of the 3 agents should be diuretic agent. The etiology of resistant hypertension is multifactorial. The first step in assessment of resistant hypertension is exclusion of pseudo-resistance. Detailed questioning on adherence to prescribed medicines and blood pressure measurement at home or ambulatory blood pressure monitoring exclude the most common causes of pseudo-resistance such as poor medication adherence and white coated hypertension.

Some medications often interfere with blood pressure control. Given their extensive use, non-steroidal anti-inflammatory drugs (NSAIDs) are the most common of such medications. These drugs worsen blood pressure control by resulting in sodium retention and vasoconstriction (1-3).

The main lifestyle factors contributing to drug-resistant hypertension are dietary sodium exposure and excess body weight. High dietary salt ingestion contributes importantly to the risk of developing hypertension but may also be a particularly important contributor to the development of resistant hypertension (4). Obesity is an independent risk factor for essential hypertension, and it also reduces benefit from pharmacologic treatment, thereby leading to an increased requirement of increased number of antihypertensive medications.

The prevalence of secondary hypertension is higher in patients with resistant hypertension than in the general hypertensive population. Renovascular disease is an important cause of secondary hypertension. Atherosclerotic renal artery stenosis (ARAS) is associated with two common clinical syndromes: renovascular hypertension and ischemic nephropathy, which often coexist. The ensuing renovascular disease constitutes the fastest-growing etiology of end-stage renal disease. Certain clues in the patient's medical history and laboratory parameters may help identify the secondary hypertension related with renovascular disease (RVD). Early or late onset of hypertension, acceleration of treated hypertension, progressive deterioration of renal function in treatments with angiotensin converting enzyme inhibitors (ACEI), repeated flush pulmonary edema, known coronary artery disease, evidence of vascular disease in the neck (bruits) or the legs (claudication), and renal asymmetry in hypertensive patients represent strong clinical indications for evaluation (5).

Diagnostic work-up for hemodynamically significant renal artery stenosis should be restricted to patients suspected to be at moderate or high risk RVD. Patients at high risk for RVD may be directly referred for renal artery angiography, the golden standard diagnostic procedure.

A renal artery stenosis with narrowing of > 60% of the lumen, is considered hemodynamically significant, and may be suitable for treatment with angioplasty or angioplasty plus stent placement. Objectives for endovascular or surgical therapy of renal artery stenosis include optimization of blood pressure control, preservation of renal function, and prevention of complications such as recurrent flash pulmonary edema (6). In our first case report, suspicion for the presence of RVD was very strong because of rapidly impaired renal functions after starting treatment with ACEI, presence of renal asymmetry, and previously

smoking habits concurrently with uncontrolled blood pressure with multiple antihypertensive agents. After successful balloon angioplasty plus stent replacement against right renal artery stenosis, antihypertensive drug requirement gradually decreased and renal functions were improved. The blood pressure is still under control with amlodipine monotherapy.

The clinical syndrome of hypertension combined with hypokalemia may be related to low renin state, such as primary hyperaldosteronism, adrenal enzyme defects, certain familial syndromes, and licorice ingestion. Primary aldosteronism is now the most common secondary cause of resistant hypertension. The prevalence of hyperaldosteronism in the hypertensive population is 5-12% (7-9), bilateral adrenal hyperplasia and aldosterone-producing adenoma are the two main causes. The diagnosis is based on the aldosterone/renin ratio as a screening test, subsequent confirmatory tests, and CT/MR imaging studies. If the aldosterone/renin ratio is increased, and plasma aldosterone concentration is appropriately elevated, 24 hour urine aldosteron measurement after sodium loading should be performed. Once the diagnosis of primary hyperaldosteronism is confirmed, CT imaging of adrenal glands should be performed to determine the subtype of primary hyperaldosteronism. Management of primary hyperaldosteronism includes surgical resection for unilateral adrenal disease and mineralocorticoid receptor antagonists for bilateral disease (10, 11). In our second case report, the patient began to have a normal blood pressure and serum potassium level after commencing spironolactone treatment. Drug resistant hypertension was improved due to blockage of aldosterone effects.

OSAS is a sleep disorder that was characterized by at least 10 apnea-hypopnea events every per hour during sleep (12, 13). Although OSAS is not a classical form of "secondary hypertension, it is commonly present in the drug-resistant hypertension, the clinical picture of which includes four main symptoms: daytime sleepiness, frequent nocturnal micro-arousals, morning asthenia with or without headache, and severe snoring (14). The use of CPAP at night time in patients with OSAS prevents sympathetic overactivity, thus improving blood pressure control (15, 16). Our third case highlights a possible association between OSAS and resistant hypertension, with a good blood pressure lowering effect after with CPAP therapy. Thus, it is reasonable to include OSAS in different diagnosis of resistant hypertension.

Conclusion

Resistant hypertension is a significant clinical problem commonly encountered by clinicians. Evaluation of a patient with resistant hypertension requires recognize of factors that contribute to pseudo-resistance to treatment, and identification of important contributing factors such as high salt intake, heavy alcohol consumption, and use of interfering medications. Secondary causes of hypertension are common in patients with resistant hypertension and should be addressed in the diagnostic workup. Treatment should include appropriate lifestyle changes and prescription of effective antihypertensive drugs.

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