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Case report

Resistant hypertension related to primary hyperaldosteronism: case report

Hipertensão arterial resistente por hiperaldosteronismo primário: relato de caso

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ABSTRACT: Resistant hypertension (RH) is a common problem. Identifying and treating patients with resistant hypertension is of paramount importance because these patients present a higher rate of target-organ damage and cardiovascular events. This report describes the case of a 54-year-old man brought to evaluation due to hematuria. He reported diagnosis of arterial hypertension 8 years ago, using 4 antihypertensive medications, including one diuretic, and good compliance to non-pharmacologic treatment. Complementary tests excluded the white coat effect and confirmed the impact of arterial hypertension on target organs. In addition, he had normal fasting glucose, thyroid and kidney function. Diagnose of RH led to screening for secondary causes of arterial hypertension, which showed a plasma aldosterone: renin activity ratio of 453. Diagnosis of primary aldosteronism was made and an imaging test demonstrated bilateral adrenal hyperplasia. A mineralocorticoid receptor antagonist was prescribed, making it possible to remove all the antihypertensive agents that had been used. Primary aldosteronism is one of the most frequent causes of secondary hypertension. However, there are evidence of substantial under screening for primary aldosteronism. Diagnosis and treating primary aldosteronism lowers blood pressure, reduces the number of antihypertensive medications required, and reduces cardiovascular events.

KEYWORDS: Hypertension; Hyperaldosteronism; Case report.

RESUMO: A hipertensão arterial resistente (HAR) é um problema clínico comum. A identificação dos pacientes portadores de HAR é de fundamental importância, uma vez que eles apresentam uma maior taxa de danos a órgãos-alvo e um risco significativamente maior de eventos cardiovasculares fatais e não fatais. Neste trabalho é relatado o caso de um paciente do sexo masculino, 54 anos, encaminhado para avaliação em função de hematúria. Tinha diagnóstico de hipertensão arterial há 8 anos, em uso de quatro classes de anti-hipertensivos. Fazia atividade física regular e negava uso de drogas ilícitas ou quaisquer outros medicamentos. Exames complementares excluíram o efeito do avental branco e confirmaram o impacto da hipertensão arterial sobre órgãos-alvo. Além disso, ele apresentava glicemia de jejum, função tireoidiana e renal normais. Diante do exposto, foi feito a hipótese diagnóstica de HAR e solicitado investigação para causas secundárias de hipertensão arterial, que evidenciou uma relação aldosterona/atividade de renina plasmática de 453. Deste modo, foi feito o diagnóstico de hiperaldosteronismo, e solicitado exame de imagem que demonstrou hiperplasia adrenal bilateral. O paciente foi orientado a iniciar espironolactona, evoluindo com rápida queda dos níveis pressóricos, sendo possível a retirada de todos os anti-hipertensivos que vinham sendo utilizados. O hiperaldosteronismo primário é uma das principais causas de HAR. Apesar dos avanços na compreensão de sua fisiopatologia, esta condição clínica segue subdiagnosticada. O diagnóstico adequado permite intervenções terapêuticas específicas, que melhoram significativamente o controle da pressão arterial e os desfechos cardiovasculares relacionados a esta condição.

PALAVRAS-CHAVE: Hipertensão arterial sistêmica (C14.907.489); Hiperaldosteronismo (C19.053.800.604); Relato de caso (V 03.100).

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INTRODUCTION

Arterial hypertension (AH) is a chronic disease characterized by a persistent elevation of blood pressure (BP), specifically systolic BP equal to or greater than 140 mmHg and/or diastolic BP equal to or greater than 90 mmHg, measured with the correct technique, on at least two different occasions and in the absence of antihypertensive medication. It is often an asymptomatic condition that can lead to structural and/or functional changes in target organs, including the heart, brain, kidneys, and vessels. AH is the main modifiable risk factor for cardiovascular diseases, chronic kidney disease and premature death, with independent and linear associations. Additionally, AH has a significant impact on medical and socioeconomic costs resulting from fatal and non-fatal complications in target organs[1-4].

Primary (or essential) AH accounts for approximately 90% of all cases of hypertension. Its pathophysiology is multifactorial, as it depends on the interaction of genetic, environmental (such as an unhealthy diet, excessive sodium intake, overweight/obesity and a sedentary lifestyle) and social factors (such as occupation, socioeconomic and cultural level, and access to the health system)[4,5].

Resistant arterial hypertension (RAH) is defined as BP that remains above the recommended goal despite the use of therapeutic strategies that include lifestyle modifications and the use of three antihypertensive drugs of different classes with synergistic effect, at optimal or maximally tolerated doses, with one of them preferably being a thiazide diuretic. If a patient requires four or more antihypertensive drugs to achieve BP control, they are considered to have resistant but controlled hypertension[5-7].

RAH is a common clinical problem faced by both primary care professionals and specialists.[8] Identifying patients with RAH is crucial, as the condition is associated with a higher rate of target organ damage and a significantly higher risk of fatal and non-fatal cardiovascular events compared to non-resistant hypertension[6,7,9]. The appropriate approach not only requires ruling out pseudo-resistance but also detecting comorbidities, target organ damage and additional cardiovascular risk factors, as well as identifying any secondary and potentially reversible causes of AH[5,6,8].

The objective of this study is to report a case of resistant arterial hypertension caused by primary hyperaldosteronism and to review its pathophysiology, diagnosis, and management. This study follows current ethical principles and has been approved by the Ethics and Research Committee of our institution (CAAE 52392721.2.0000.0037).

CASE REPORT

A 54-year-old male patient was referred for a nephrological evaluation due to the presence of microscopic hematuria detected during a routine examination. Ultrasound examination of the prostate and bladder revealed no evidence of abnormalities.

The patient had no other complaints.

The patient had been hypertensive since the age of 48 and was using several antihypertensive drugs on a daily and regular basis. He had already tried several different medications, but most of the time he used at least four classes of antihypertensive drugs (calcium channel blocker, angiotensin 2 receptor blocker or angiotensin-converting enzyme inhibitor, beta blocker, and diuretic).

In terms of family history, the patient's mother had hypertension that was controlled with two medications. His father died at the age of 40 due to liver disease.

The patient denied smoking or alcohol use and reported regular physical activity (at least 60 minutes per day, 5 times per week) and low sodium intake. He also denied using illicit drugs or any other medication, except for antihypertensives.

Physical examination revealed a body mass index of 22.7Kg/m^2 and a heart rate of 60bpm. BP was measured in both upper limbs and was 150x100mmHg. No carotid or abdominal murmurs were detected.

The patient's urinalysis showed non-glomerular hematuria, which resolved on its own. The 24-hour urine collection revealed 210mg of proteinuria. An ultrasound revealed a small simple renal cyst in the right kidney, with a recommendation for clinical monitoring.

A transthoracic echocardiography showed concentric hypertrophy of the left ventricle (LV) with diastolic dysfunction (diastolic thickness of the interventricular septum of 12mm; LV posterior wall of 11mm; LV end-diastolic volume of 107.52ml and ejection fraction of 70.04%).

Ambulatory blood pressure monitoring (ABPM) showed total pressure load of 68% and 90% (percentage of waking and sleeping measurements above 135/85 and 120/70, respectively).

Biochemical tests showed normal fasting glucose, normal thyroid and renal function, and potassium level of 4.3mmoL/L.

Based on these findings, a diagnostic hypothesis of RAH was suggested and further investigation for secondary causes of AH was requested.

Doppler ultrasonography of the renal arteries and measurement of urinary metanephrines were within normal limits. Plasma renin activity (PRA) was 0.1ng/mL/h and plasma aldosterone (PAC) was 45.3ng/dL. As the PAC/PRA ratio > 100, the diagnosis of hyperaldosteronism was made. An abdominal tomography was performed subsequently and showed bilateral adrenal hyperplasia.

The patient was advised to start taking spironolactone (50mg/day), which resulted in a rapid decrease in blood pressure levels, allowing for the discontinuation of all antihypertensive drugs except for the beta-blocker, which

was maintained due to the previously diagnosed cardiac dysfunction.

Examinations carried out two years after the start of treatment showed negative proteinuria and potassium of 4.9mmoL/L. Echocardiography showed a reduction in the diastolic thickness of the interventricular septum (9mm) and of the LV posterior wall (9mm), with an LV end-diastolic volume of 108ml and an ejection fraction of 67%.

DISCUSSION

RAH is a growing public health concern. Although the exact prevalence is unknown, population research suggest that RAH is not uncommon, affecting up to 20% to 30% of hypertensive patients, depending on the population studied and the level of medical screening. Moreover, it is believed that this prevalence may rise significantly due to factors such as increased life expectancy, high rates of obesity, diabetes mellitus and obstructive sleep apnea, and unhealthy lifestyle habits (such as excessive salt intake)[6-9].

The largest study on this topic in Brazil was published in 2018 and evaluated patients from 26 centers using ambulatory blood pressure monitoring (ABPM), revealing a prevalence of RAH of 11.7%[9].

The evaluation of patients with suspected RAH should aim to confirm true treatment resistance, identify causes contributing to resistance, including secondary causes of hypertension, and document any target organ damage that can support a diagnosis of poorly controlled hypertension.[8]

Pseudo-resistance refers to the inability to control BP due to white-coat hypertension, errors in BP measurement techniques, or non-adherence to prescribed pharmacological and non-pharmacological treatment[6].

Poor adherence to treatment is one of the main causes of uncontrolled BP and is quite common in primary care[8]. Patients should be asked specifically about their adherence to prescribed measures without being judged. The problems related to patients include reluctance to take an excessive number of drugs with complex dosages, drug side effects, socio-cultural issues, and lack of knowledge about the history of the disease. Adherence can also be influenced by factors related to healthcare professionals and services, such as poor doctor-patient relationships and difficulty accessing multidisciplinary teams, medications, and complementary tests. It is also important to inquire patients about salt intake and, if possible, measure it with a 24-hour urine sodium test[6].

Accurate diagnosis of RAH relies on the use of proper BP measurement technique in the medical office. The precautions that should be taken include having the patient sit in a comfortable and silent environment for 5 minutes before measuring and ensuring that the individual has not engaged in physical activities in the last hour, or ingested alcohol, coffee or food, or smoked in the previous 30 minutes. In addition, an appropriate cuff size for the patient's arm circumference should be used, and at least 3 measurements with intervals of 1 to 2 minutes should be taken on the reference limb[5,8].

Measurement of BP outside of the medical office is crucial to confirm the diagnosis of RAH, which can be done through ABPM or HBPM (home blood pressure monitoring), respecting their indications and limitations. The primary differential diagnosis for RAH is white-coat hypertension, a condition where BP is elevated in the medical office but normal outside of it.[5] Studies suggest that a significant white-coat effect (when blood pressure is persistently elevated in the clinic, while out-of-office values are normal or significantly lower) is as common in patients with RAH as in the general hypertensive population, with a prevalence of 20% to 30%. Additionally, ABPM or home BP measurements have a stronger correlation with unfavorable cardiovascular outcomes than casual BP measurements[6,8].

In the case presented, the hypothesis of pseudo-resistance was ruled out as the patient reported good adherence to treatment and the ABPM results showed a high total BP, indicating that the uncontrolled BP observed in the consultation was not solely due to the white-coat effect.

After ruling out pseudo-resistance, it is important to identify potential causes of treatment resistance, such as obesity and certain medications, and evaluate the presence of secondary etiologies of hypertension, according to clinical suspicion[6-8].

Several medications have been associated with increased blood pressure, including non-steroidal anti-inflammatory drugs, oral contraceptives, sympathomimetics (such as nasal decongestants, appetite suppressants and cocaine), chemotherapy drugs, antidepressants, erythropoietin, immunosuppressants and alcohol[5].

The absence of any apparent cause that could be contributing to treatment resistance in the patient described in the case report, along with the presence of signs of target organ damage associated with AH (echocardiographic changes and proteinuria), led to the decision to investigate potential secondary causes of hypertension.

Secondary arterial hypertension is characterized by AH with an identifiable cause, which can be treated with a specific intervention that leads to cure or improvement of blood pressure control. The prevalence of secondary AH is estimated to be between 10 and 20%, depending on the population studied, the availability of diagnostic resources, and the experience of the healthcare providers[4,5]. Secondary causes of AH are more common in patients with resistant AH than in those with non-resistant AH. The most common causes are obstructive sleep apnea (80%), followed by hyperaldosteronism (6-23%), renovascular disease (renal artery stenosis) (2.5-20%) and renal parenchyma disease (2 to 10%). Investigating thyroid function abnormalities (1-3%) is also recommended[5,6].

The identification of secondary AH is crucial, as it is associated with higher risk of cardiovascular and renal complications and greater impact on target organs due to sustained elevated BP levels and activation of hormonal and molecular mechanisms[10,11]. Patients may present with other signs and symptoms suggestive of a specific etiology of secondary AH. For example, daytime sleepiness, reports of snoring and breathing pauses may suggest obstructive sleep apnea. A history of peripheral or coronary atherosclerotic disease, with or without an abdominal murmur, increases the likelihood of renal artery stenosis. Labile hypertension associated with palpitations and/or diaphoresis may indicate pheochromocytoma[8]. Therefore, in addition to considering the epidemiologically common causes, the investigation should take into account evidence from the patient's clinical history, physical examination, and complementary tests[5,10,12].

Primary hyperaldosteronism is a clinical syndrome characterized by the autonomous production of aldosterone. The main causes of primary hyperaldosteronism are aldosterone-producing adenomas and bilateral adrenal hyperplasia. Less common causes include genetically determined forms (familial hyperaldosteronism types I to IV), unilateral adrenal hyperplasia, aldosterone-producing adrenal carcinomas, and ectopic aldosterone-producing tumors[13].

Older studies found that primary hyperaldosteronism affected less than 1% of hypertensive patients. However, studies published within the last 15 years have documented a considerably higher prevalence, with values ranging from 5 to 10% among hypertensive patients, and up to 23% in populations with RAH, depending on the criteria used for screening[6,14-18].

Several national and international medical societies, including the Brazilian Society of Cardiology, the American Heart Association, the American College of Cardiology, the Endocrine Society, and the European Society of Hypertension, recommend screening individuals with RAH for primary hyperaldosteronism using the PAC/PRA ratio[7,18,19]. To ensure accurate interpretation of the test results, it is advised that patients avoid using mineralocorticoid antagonists for at least 4 weeks before the collection, and that plasma aldosterone levels are at least 10 ng/dL. A PAC/PRA ratio below 30 is the most common reference value for ruling out the diagnosis of hyperaldosteronism. A ratio greater than or equal to 100 is considered sufficient to confirm the diagnosis. In this case, imaging tests (abdominal CT scan or MRI) and referral to a hypertension specialist or endocrinologist for further evaluation and treatment are recommended. If the PAC/PRA ratio is in the intermediate range, the recommendation is to continue the investigation with additional tests, such as the volume infusion test[6,8,18,19].

Despite being commonly reported in the literature, hypokalemia has a low negative predictive value for the diagnosis, as it is reported in 30 to 60% of patients[19].

The patient described had a potassium level of 4.3mmoL/L, plasma renin activity (PRA) of 0.1ng/mL/h and plasma aldosterone (PAC) of 45.3ng/dL, resulting in an PAC/PRA ratio of 453. Therefore, the diagnosis of hyperaldosteronism was confirmed, and a CT scan of the abdomen was requested, which showed bilateral adrenal hyperplasia.

Despite the growing awareness about primary hyperaldosteronism, this condition is still believed to be underdiagnosed. A recent multicenter study conducted in North America evaluated the clinical management of over 269,000 patients with RAH between 2000 and 2017 and found low rates of hyperaldosteronism screening (1.6% of patients) across all centers analyzed, with no improvement over time. Patients evaluated by a nephrologist (hazard ratio [HR], 2.05 [95% CI, 1.66 to 2.52]) or an endocrinologist (HR, 2.48 [CI, 1.69 to 3.63]) were more likely to be tested for primary hyperaldosteronism than those seen in primary care. The patients who were tested had higher percentages of mineralocorticoid receptor antagonist use (HR, 4.10 [CI, 3.68 to 4.55]) and better BP control. These findings demonstrate the importance of educating healthcare professionals about the importance of conducting appropriate tests for the diagnosis of primary hyperaldosteronism and recognizing increased renal and cardiovascular morbidity, which can be reversed with appropriate treatment[20].

Another study published recently evaluated 4660 individuals with RAH aged between 18 and 90 years, from 2008 to 2014, and found a screening rate for primary hyperaldosteronism of 2.1% (24-month follow-up). Patients who were screened for primary hyperaldosteronism were significantly younger (55.9±13.3 versus 65.5±11.6 years; $P < 0.0001$), had higher systolic and diastolic BP levels [(145.1±24.3 versus 139.6±20.5 mm Hg; $P = 0.04$) and (81.8±13.6 versus 74.4±13.8 mm Hg; $P < 0.0001$), respectively], and lower serum potassium levels (3.9±0.6 versus 4.1±0.5 mmol/L; $P = 0.04$)[21].

The management of primary hyperaldosteronism depends on the etiology diagnosed. Surgical resection is recommended in cases of aldosterone-producing adenoma or unilateral adrenal hyperplasia, while clinical treatment with a mineralocorticoid receptor antagonist is recommended for patients with bilateral adrenal disease[6,18].

Finally, it is important to note that patients with primary hyperaldosteronism have a higher incidence of cardiovascular morbidity and mortality when compared to patients with primary hypertension and similar BP levels.[22-26] A meta-analysis of 31 studies involving 3838 patients with primary hyperaldosteronism and 9284 patients with primary hypertension found an increased risk of stroke (OR 2 .58), coronary artery disease (OR 1.77), atrial fibrillation (OR 3.52) and heart failure (OR 2.05) in patients with aldosterone-producing adenomas and bilateral adrenal

hyperplasia[27]. Additional evidence demonstrating the negative cardiovascular effects of excess aldosterone has been provided by randomized controlled trials that found improved survival rates with the use of mineralocorticoid receptor antagonists (spironolactone and eplerenone)[28,29].

As the patient described in this study had bilateral adrenal disease, he was treated with spironolactone, which resulted in significant improvement in blood pressure control and in the previously documented target-organ damage (negative proteinuria and reduction in the diastolic thickness of the interventricular septum and LV posterior wall).

CONCLUSIONS

The evaluation of patients with clinically suspected RAH should focus on confirming true treatment resistance, documenting target organ damage, and identifying causes contributing to treatment resistance, including secondary causes of hypertension.

Primary hyperaldosteronism is one of the main causes of secondary AH. Despite advances in understanding its pathophysiology, this condition remains underdiagnosed. Proper diagnosis allows for specific therapeutic interventions, which significantly improve blood pressure control and adverse cardiovascular outcomes related to this clinical condition.

We believe that this study can contribute to highlighting the importance of screening patients who exhibit clinical features that suggest secondary AH and using available resources judiciously for this purpose.

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