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MINI REVIEW ARTICLE

Resistant Hypertension

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ABSTRACT

Resistant hypertension is defined as persistent elevation of office blood pressure (BP) above the appropriate goal of therapy (>140/90 mmHg in most of hypertensive patients or >130/80 for those with ischemic heart disease, diabetes, or renal insufficiency) despite the use of maximally tolerated doses of three or more different classes of antihypertensive agents, including a diuretic. It is also defined as controlled blood pressure on at least 4 antihypertensive medications. Its true prevalence is <10% of treated patients after exclusion of causes of pseudo-resistant hypertension. Patients are at higher risk of hypertension mediated organ damage, chronic kidney disease, and premature cardiovascular event. True resistant hypertension should be differentiated from pseudo-resistance hypertension due to poor measurement technique, suboptimal blood pressure control secondary to medication non-adherence, white coat effect, high salt intake, excess alcohol consumption, uncontrolled obesity, continuous stressful exposure, lack of exercise. Causes of secondary hypertension must be ruled out. Resistant hypertension should be confirmed by out off office blood pressure measurements either by home blood pressure or ambulatory blood pressure measurements.

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KEYWORDS Resistant hypertension, Medication adherence, Spironolactone.

Introduction

Resistant hypertension (RH) is defined as persistent elevation of office blood pressure (BP) above the recommended goal of therapy (>140/90 mmHg in most of hypertensive patients or >130/80 for those with ischemic heart disease, diabetes, or renal insufficiency despite the use of maximally tolerated doses of three or more different classes of antihypertensive agents, including a diuretic. It is also defined as controlled blood pressure on at least 4 antihypertensive medications. True resistant hypertension should be differentiated from pseudo-resistance hypertension due to suboptimal blood pressure control secondary to medication non-adherence, white coat effect, high salt intake, excess alcohol consumption, uncontrolled obesity, and continuous stressful exposure, lack of exercise or poor measurement technique [1].

Prevalence

Its true prevalence is <10% of treated patients after exclusion of causes of pseudo-resistant hypertension. Patients are at higher risk of hypertension mediated organ damage, chronic kidney disease, and premature cardiovascular event [2].

Diagnosis

Diagnosis of resistant hypertension requires ruling out causes of pseudo-resistance hypertension[1] and causes of secondary hypertension, as volume overload (due to excessive sodium intake, inadequate diuretic therapy and/or progressive chronic kidney disease) [1], drug induced resistant hypertension as non-steroidal anti-inflammatory drugs, glucocorticoids, estrogen containing contraceptives, sympathomimetics, erythropoietin-stimulating agents, calcineurin inhibitors (cyclosporine, tacrolimus) [1]. Renal parenchymal disease which lead to upregulation of renin-angiotensin aldosterone system, increased salt and fluid retention, increased sympathetic nervous system activity and endothelial dysfunction [3]. Primary aldosteronism leads to salt and water retention and renal potassium wasting. It is common and usually goes undiagnosed, with a prevalence ranging from 8% to 30% [4]. Hypokalemia is present in only 9% to 37% of patients who have primary aldosteronism [4]. Obstructive sleep apnea is very common and it should be ruled out in patients with resistant hypertension. It increases upper-airway resistance, leading to hypoxia, and hypercapnia. Renovascular hypertension is a syndrome of elevated blood pressure due to diminished renal arterial blood flow resulting in kidney ischemia [1]. Atherosclerosis of the renal arteries is the main cause, but other pathologic processes include fibromuscular dysplasia, renal artery infarct or dissection, and vasculitis can cause hypertension. Endocrinopathies include pheochromocytomas and paragangliomas are rare causes of hypertension, accounting for 0.2% to 0.6% of cases, but are associated with significant mortality risk [5]. Cushing disease is a relatively uncommon cause of resistant hypertension. Less common disorders include thyroid and parathyroid glands. Testing for primary hyperparathyroidism should be considered in any patient presenting with increased potassium level [1].

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Treatment

Treatment of RH includes, exclusion of causes of secondary hypertension based on history, physical findings, and individual risk factors. A multifactorial approach to treat resistant hypertension includes a combination of lifestyle modification, pharmacotherapy and using single pill combination treatment is recommended to reduce pill burden and improve adherence to treatment, then identifying comorbidities that require first-line agents that have a compelling indication, such as beta-blockers for heart failure, history of myocardial infarction, or aortic dissection, or drugs that block the renin- angiotensin-aldosterone system for proteinuria. The initial pharmacologic approach to resistant hypertension consists of 3 medications, each is mechanistically different and at maximally tolerated doses. This includes ACE inhibitors or ARB, long-acting dihydropyridine calcium channel blocker and diuretic in patients with preserved glomerular filtration rate (GFR). The preferred first-line diuretic is either chlorthalidone or indapamide because of their longer half-life and more potent antihypertensive effect compared with hydrochlorothiazide[6]. If blood pressure is still not controlled on maximally tolerated therapy with these 3 agents, a mineralocorticoid receptor antagonist (MRA) (spironolactone 25-50 mg/d or eplerenone (50 - 100 mg/day) should be the fourth-line agent. The PATHWAY-2 trial demonstrated that spironolactone was superior in reducing blood pressure compared with bisoprolol, doxazosin, or placebo as add-on therapy in patients with resistant hypertension on 3 blood pressure medications [7]. However, use of MRA has a major limitation to treat patients with RH and chronic kidney disease (CKD) due to occurrence of hyperkalemia. This risk increases when eGFR is <45 mL/min/1.73 m^2 and/or when serum potassium is >4.5 mmol/L prior to the initiation of therapy[8]. The risk of all-cause mortality increases at potassium levels ≥5.2 mmol/L with progressively increased risk as potassium levels rise beyond that level [9]. Two possible policies are recently being advised for patients with RH and CKD in whom MRAs are relatively or absolutely contraindicated: (1) using a new potassium binding agent to enable use of an MRA [9,10] or (2) use of a novel nonsteroidal MRA, such as finerenone or esaxerenone with lower incidence of hyperkalemia compared to steroidal MRAs[11,12].

Recently, the development of aldosterone synthase inhibitors (ASI) has shown promise in treating hypertension by decreasing aldosterone production and can potentially serve as an alternative to MRAs in RH. Baxdrostat[13] & Lorundrostat [14], newer highly potent ASI, have revealed promising results in recent trials and are currently undergoing phase 3 trials. Earliest findings have shown their effectiveness in treating patients with RH, aiming for better blood pressure control and management.

The addition of other agents should be based on individual factors; beta-blockers may be the preferred fifth-line agent [1]. Other choices include: doxazosin centrally acting alpha-1 antagonist can be used when spironolactone is contraindicated or not tolerated or clonidine, a centrally acting alpha-2 agonist can be given as a transdermal patch to improve adherence, minimize frequent oral dosing, and lower the risk of rebound hypertension [1]. If blood pressure is still not at goal, hydralazine may be initiated at a starting dose of 25 mg 3 times a day, with the addition of a nitrate in the presence of heart failure with reduced ejection fraction[1]. Finally, minoxidil may be used if hydralazine is not tolerated. Hydralazine and minoxidil are associated with fluid retention and reflex tachycardia [1].

Renal denervation to blunt sympathetic tone showed no benefit in the Renal Denervation in Patients with Uncontrolled Hypertension (SYMPLICITY HTN-3) study[15]. The Study of the ReCor Medical Paradise System in Clinical Hypertension (RADIANCE-HTN TRIO) [16], utilizing a newer catheter design and a strict medication protocol, demonstrated a decrease of 5.8 mm Hg compared with controls, a modest benefit. Carotid baroreceptor activation therapy and carotid baroreceptor amplification therapy (aimed at sympathetic tone modulation). None of these device therapies are currently FDA-approved, and more studies are needed to determine their long-term efficacy and safety.

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