Resistant Hypertension: Current Status, Future Challenges

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ABSTRACT

Resistant hypertension in adolescents is increasing in frequency and is increasingly recognized as having significant short- and long-term health consequences. It may be seen in up to 30% of all hypertensive patients cared for. Adolescents with resistant hypertension are at higher cardiovascular (CV) risk due to a long history of severe hypertension complicated by other CV risk factors such as obesity. Common causes of resistant hypertension include primary aldosteronism, sleep apnea, diabetes and chronic kidney disease. Careful blood pressure (BP) measurement and thorough evaluation of patients with sustained BP elevation should make a possible early diagnosis of resistant hypertension. Successful treatment requires identification and reversal of life-style factors contributing to treatment resistant and diagnosis and appropriate treatment of causes of hypertension. Improved pharmacologic therapies may offer the potential for preventing or at least ameliorating early CV disease. This review highlights these and other important issues in the evaluation and management of adolescents with resistant hypertension and provides practical guidance to the practitioners involved in caring for such patients.

Keywords: Cardiovascular disease, children and adolescents, prevention, resistant hypertension

Review Article

INTRODUCTION

Hypertension is a major public health problem world-wide. It imposes a large burden on society that is growing larger in terms of mortality or morbidity, quality-of-life and costs.[1] Resistant hypertension is defined as persistent elevation of blood pressure (BP) above the goal in spite of concurrent use of three to four antihypertensive agents of different classes at maximally tolerated doses including a diuretic.[2,3] Resistant hypertension does not necessarily mean uncontrolled hypertension. As defined, resistant hypertension may also include patients whose BP is controlled with the use of more than three medications. Patients with resistant hypertension are at increased risk of stroke, cardiovascular (CV) disease, and chronic kidney disease (CKD).[2-5] Secondary hypertension is more common in children than in adults. Hence resistant hypertension should be more common in children.

EVALUATION

The diagnosis of resistant hypertension requires optimal BP measurement techniques to confirm persistently elevated BP readings. Pseudoresistance hypertension, including patients who lack BP control secondary to inaccurate suboptimal treatment regimen, poor adherence to antihypertensive therapy, life-style and diet, use of anti-inflammatory agents or white coat hypertension, must be excluded.[2,6-8] Ambulatory BP monitoring or home BP allows the identification of white coat effect.[6]

Among the most common secondary causes of resistant hypertension are primary hyperaldosteronism, renal vascular hypertension, CKD, diabetes and sleep apnea.[9] Less common causes include pheochromocytoma and aotic coarctation.[2]

Primary hyperaldosteronism presents in approximately 20% of patients with resistant hypertension.[2,9] In general, plasma renin activity (PRA) is very low or undetectable in patients with primary aldosteronism. Furthermore, in most patients with primary aldosteronism, the plasma aldosterone concentration is >15 ng/dL. In general, PRA is very low or undetectable in patients with primary aldosteronism. Furthermore, in most patients with primary aldosteronism, the plasma aldosterone concentration is >15 ng/dL. A plasma aldosterone level (ng/dL)/PRA (ng/mL/h) ratio of greater 20 is likely suggestive of primary hyperaldosteronism but further investigation is required to confirm the diagnosis.[10]

A high suspicion for primary hyperaldosteronism should be entertained for patients with following clinical history: Spontaneous or unprovoked hypokalemia with renal potassium wasting, diuretics-induced hypokalemia that does not normalize after discontinuation of diuretics for at least 4 weeks and is unresponsive to angiotensin blockers and a family history of primary hyperaldosteronis.[9,10] In a study of patients with resistant hypertension versus control subjects, plasma aldosterone levels, aldosterone-to-renin ratio and 24-h urinary aldosterone levels all were significantly higher in patients with resistant hypertension.[10] Experts recommend screening patients with resistant hypertension for plasma aldosterone and 24-h urinary aldosterone levels, as well as PRA, even if the serum potassium level is normal.[11]

In addition, patients with resistant hypertension should be evaluated for pheochromocytoma if they have suggestive manifestations such as episodic hypertension, palpitations and/or diaphoresis or tremor and if all else is negative, it is reasonable to begin an evaluation for renal artery stenosis.[2]

Adrenal vein sampling (AVS) is considered the gold standard for localizing aldosterone-producing adenomas in patients with primary hyperaldosteronism.[12] Most of patients with an aldosterone producing adenoma (APA) will have cortisol-corrected aldosterone lateralization ratios greater than 4.0. In addition, the contralateral aldosterone to cortisol ratio is less than the inferior vena cava aldosterone to cortisol ratio in 93% of patients with surgically confirmed APA.[2,9-12]

It has been shown to have an accuracy rate as high as 96.6% and also has altered the course of clinical management in about 37.5% of patients.[12] Following the AVS, an aldosterone-blocking agent can be added to test therapeutic response. AVS is recommended for patients with primary aldosteronism when the computed tomography scan is normal, shows bilateral abnormalities, or shows a unilateral abnormality who would like to pursue surgical management (unilateral adrenalectomy).[2-9,12]

TREATMENT OPTIONS

Adding a mineralocorticoid receptor antagonist, such as spironolactone or epleronone, has been shown to reduce resistant hypertension in patients with primary aldosteronism especially those with bilateral adrenal hyperplasia, which has been found to be a contributing factor in about two thirds of cases of primary aldosteronism.[13,14] In this study, spironolactone reduced systolic BP by as much as 25 mm Hg when added to a multidrug regimen that included a diuretic and an angiotensin converting enzyme (ACE) inhibitor or angiotensin-receptor blockade (ARB) and the reduction was seen in patients with and without primary aldosteronism [Table 1].[13] Similar results were seen in a smaller study of patients with hypertension that was not responding to at least a dual therapy.[15]

Studies combining an ACE inhibitor with an ARB have produced varied results, and one has stirred controversy. The COOPERATE trial showed the combination of an ACE inhibitor and

Table 1: Antihypertensive drugs for management of resistant hypertension in children and adolescents

Class	Drug	Recommended doses
Aldosterone antagonist	Spironolactone†	1-3 mg/kg/day QD up to 100 mg/day
	Eplerenone†	25 mg/day QD-BID up to 100 mg/day
ACE inhibitors	Captopril†	0.3-6 mg/kg/day BID-TID up to 450 mg/day
	Enalapril†	0.08-0.6 mg/kg/day up to 40 mg/day
	Lisinopril†	0.07-0.6 mg/kg/day up to 40 mg/day
Angiotensin-receptor blockers	Losartan	0.7-1.4 mg/kg/day up to 100 mg/day
β-adrenergic antagonists	Propranolol	1-16 mg/kg/day BID-TID up to 640 mg/day
	Atenolol	0.5-2 mg/kg/day up to 50 mg/day
Calcium channel blockers	Isradipine§	0.05-0.8 mg/kg/day TID-QID up to 20 mg/day
	Amlodipine§	0.06-0.3 mg/kg/day QD up to 10 mg/day
	Felodipine§	2.5 mg/day up to 10 mg/day
Diuretics	Hydrochlorothiazide‡	0.5-3 mg/kg/day up to 50 mg/day
	Furosemide‡	0.5-6 mg/kg/day

QD=Once daily, BID=Twice daily, TID=Three times daily, QID=Four times daily, ACE=Angiotensin converting enzyme, †Monitor serum creatinine and potassium levels, monitor heart rate; avoid in infants with bronchopulmonary dysplasia and heart failure, §May cause reflux tachycardia and fluid retention, ‡Monitor serum electrolytes

ARB to be superior to ACE-inhibitor monotherapy in slowing the progression of non-diabetic renal disease.[16] Other trials also have called into question the effectiveness and/or safety of dual renin-angiotensin system (RAS) blockade in the treatment of hypertension associated with heart failure or CV disease.[17] Until studies demonstrate true benefit, experts recommend avoiding dual RAS blockades.[18,19]

A recent systematic review suggested that treatment with beta-blockers improved all-cause mortality in patients with CKD and heart failure.[20]

Recent studies recommends treating patients with resistant hypertension who are unresponsive to aggressive antihypertensive therapy with ablation of sympathetic nerves in the renal arteries.[21,22] These studies also suggest that renal sympathetic denervation provides safe and sustained BP reduction up to 1 and 2 years.[21-23]

CONCLUSIONS

Resistant HTN is usually due to poor compliance, suboptimal therapy, renal vascular hypertension, or use of NSAID, oral contraceptives, steroids, and estrogen replacement therapy. Primary hyperaldosteronism, renal vascular hypertension, and CKD are the most common secondary causes of resistant hypertension.

A combination of ACE-inhibitor, ARB, plus a beta a blocker, and/or calcium channel blocker are highly effective and have an additive effect, controlling BP in up to 85% of patients. Aldosteron antagonist may be added in patients with primary hyperaldosteronism. Thiazide or loop diuretic is often indicated in edematous states including patients with heart failure or chronic kidney disease. Renal nerve ablation is preserved for patients who fail to response to aggressive antihypertensive drug therapy.

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