

INTRODUCTION

There have been considerable advances in the pharmacotherapy of hypertension, we now have a variety of antihypertensive drugs specifically targeting the different biochemical, hormonal and hemodynamic factors involved in the pressor mechanism. Despite this and the advances in our knowledge about the pathophysiology, we clinicians continue to face problems in attaining acceptable level of blood pressure control leading to serious target organ damage, followed by increased morbidity and mortality. Although the exact incidence of resistant hypertension is not known, with the population growing older and heavier it is only likely for it to go up. The importance of diagnosis of resistant hypertension also lies with the fact that we could sometimes unearth a reversible cause of hypertension. This article aims to update our present knowledge of what is called as resistant hypertension – its definition, aetiology, evaluation and management.

Traditionally, resistant hypertension is defined as blood pressure that remains above goal in spite of the concurrent use of three antihypertensive of different classes, one of which should be a diuretic and all agents being used in optimal doses.

By definition, the diagnosis also includes patients whose BP is controlled with the use of more than three medications.

Uncontrolled hypertension is not synonymous with

Table 1: Drugs that contribute to treatment resistance

- Nonnarcotic Analgesic – NSAID, COX 2 Inhibitors
- Sympathomimetic agents – Decongestants, Cocaine
- Stimulants – Methylphenidate, dexamethylphenidate, dextroamphetamine, amphetamine, methamphetamine, modafinil
- Alcohol
- Oral Corticosteroids – Especially cortisone and hydrocortisone which have the greatest mineralocorticoid effect
- Oral Contraceptive
- Cyclosporine
- Erythropoietin
- Herbal compounds – Ephedra or ma huang
- Licorice – Ingredient in oral tobacco products, suppresses metabolism of cortisol.

Most cases of true resistant hypertension are albeit due to secondary hypertension.

resistant hypertension. Before labeling as resistant hypertension based on the above criteria, the following provisions need to be applied and exclude uncontrolled hypertension due to

- Poor adherence,
- Inadequate treatment regimen – the drug, its frequency and dosage,
- Pseudo resistance.

Populations with resistant hypertension usually have multiple disease process and most have secondary hypertension. Presence of obesity, excessive salt intake, sleep apnea and renal diseases being particularly common factors. Strict implementation of therapeutic life style changes, reemphasizing compliance; recognition and treating the secondary causes of hypertension and judicious use of combination anti-hypertensives are imperative for successful treatment outcomes.

PREVALENCE

In our setting considering the prevalence of diabetes, increased salt intake, recurrent urinary tract infection, and abuse of NSAIDs – the renal parenchymal disease appears to play a major role. Additionally, in view of the increased prevalence of tropical aortoarteritis and the atherosclerosis – renal artery stenosis contributes to renovascular hypertension. A high index of suspicion and detailed clinical examination followed by specific hormonal test and imaging will help in identifying the endocrine causes of which primary aldosteronism is often missed and occasionally pheochromocytoma.

The prevalence and the genetic assessment of patient with resistant hypertension are very limited.

PSEUDORESISTANCE

It is important to adhere to basic principles of medicine and advocate proper technique in measuring the blood pressure, consider white-coat effect and reemphasize and confirm adherence to treatment before labeling such of the patients as resistant hypertension.

The three main parameters contributing to resistant hypertension are:

- Life style
- Drugs (Table 1)
- Secondary Hypertension (Table 2)

Life style factors like Obesity, excess ingestion of dietary salt, smoking and heavy alcohol indulgences are all associated with increased risk of resistant hypertension.

Table 2: Clinical & Laboratory Clues of Secondary Hypertension

Findings	Disorder Suspected	Further Diagnostic Studies
Snoring, daytime somnolence, obesity, unexplained fatigue	Obstructive sleep apnea	Polysomnography
Hypokalemia, hypernatremia	Aldosteronism	Ratio of plasma aldosterone to plasma renin activity, CT scan of adrenal glands
Edema, elevated blood urea nitrogen and creatinine levels, proteinuria	Renal parenchymal disease	Creatinine clearance, renal ultrasonography, Renal biopsy
Abdominal bruit	Renovascular disease	Magnetic resonance angiography, renal arteriography
Young adult, Headache, claudication in legs, Decreased or delayed femoral pulses, Murmurs in the precordium	Coarctation of aorta	CXR – Inverted Figure of 3 notching of ribs, Doppler or CT imaging of aorta
Weight gain, fatigue, weakness, hirsutism, amenorrhea, moon facies, dorsal hump, purple striae, truncal obesity, hypokalemia	Cushing's syndrome	Iatrogenic Cushing's commoner. Dexamethasone-suppression test
Paroxysmal hypertension, headaches, diaphoresis, palpitations, tachycardia	Pheochromocytoma	Urinary catecholamine metabolites (vanillylmandelic acid, metanephrines, normetanephrines) Plasma free metanephrines
Fatigue, weight gain, hair loss, diastolic hypertension, muscle weakness	Hypothyroidism	Thyroid Function Test
Heat intolerance, weight loss, palpitations, systolic hypertension, exophthalmos tremor, tachycardia	Hyperthyroidism	Thyroid Function Test
Kidney stones, osteoporosis, depression, lethargy, muscle weakness – the classical description of Bone, moan, stone, groan!	Hyperparathyroidism	Serum calcium, parathyroid hormone levels
Headaches, fatigue, visual problems, enlargement of hands, feet, tongue	Acromegaly	Growth hormone level

Table 3: Problems in measurement of BP

When the patient has	BP appears higher by
1. Cuff over clothing & Wrong Cuff Size	10 – 40 mm of Hg
2. Full Urinary bladder	10 – 15 mm of Hg
3. Unsupported arm	10 mm of Hg
4. Unsupported back or feet	5 – 10 mm of Hg
5. Crossed legs	2 – 8 mm of Hg

EVALUATION

A detailed medical history is important and should include the documentation of duration, severity and progression of hypertension, with any target organ involvement. Detailed drug history including the response to prior medication including their adverse effects, if any, should be noted. Specific vital information could include the level of adherence and the intake of over the counter and other alternative forms of therapy, this piece of information is a bit tricky and to be elicited in a non judgmental fashion or with out being very critical, seeking the assistance of family members may clear some ambiguities but should be done in the presence of the patient.

A history of snoring, and daytime somnolence increases

the possibility of sleep apnea, history of peripheral vascular disease or cardiovascular disease increases the possibility of renal artery stenosis; a labile hypertension associated with palpitation and diaphoresis suggests Pheochromocytoma.

It will be seen from the above list, that a good proportion account for curable causes – Secondary hypertension, in contrast to the Primary or Essential hypertension, which can only be controlled but not curable

EXAMINATION

Strict adherence to basic technique of blood pressure measurement is essential.

Common problems accounting for inaccurate BP measurements are listed in Table 3.

The emerging strategies to assess hypertension includes Self-measured home BP and 24-hour – ambulatory blood pressure. These are useful adjuncts to office BP measurements especially in detecting

- 'White Coat' hypertension and White coat worse' hypertension
- Assessing the nocturnal blood pressure which may be a more important predictor of cardiovascular events

Table 4: Summary	
Confirm RHTN	<ul style="list-style-type: none"> • > 140/90; > 3 Drugs in optimal dose; One diuretic • BP Optimal Control but using > 3 drugs
Exclude Pseudoresistance	<ul style="list-style-type: none"> • Improper Technique • Poor Compliance • White Coat Phenomenon
Reversible Factors	<ul style="list-style-type: none"> • Obesity, Physical Inactivity • Excess Salt consumption • Alcohol excess • Drugs - NSAIDs, OCPs, Sympathomimetics, Stimulants
Rule out Secondary HTN	<ul style="list-style-type: none"> • Obstructive Sleep Apnea • Primary Aldosteronism • CKD Renal Artery Stenosis • Pheochromocytoma Cushing's Syndrome • Coarctation of Aorta
Pharmacotherapy	<ul style="list-style-type: none"> • Optimise diuretic therapy including the use of aldosterone antagonist • Use agent with different yet complimentary mechanism of action • Specialist referral in compelling indications

- Uncover 'masked hypertension'

MANAGEMENT

Aim

Prompt and effective treatment with strict life style measures, judicious use of medications and or surgical interventions to quickly attain near normal blood pressure to prevent further target organ damage

Steps

1. Advocating strict healthy life style measures like regular exercises, restriction of salt, weight reduction, moderation of alcohol intake and complete abstinence from smoking
2. Discontinuance of drugs likely to increase blood pressure
3. Screen for secondary causes of hypertension and institute specific treatment and possible cure
4. Judicious use of pharmacotherapy advocating effective combinations in optimal doses
5. In refractory cases renal sympathetic denervation and baroreceptor activation therapy have been tried but have not shown to be beneficial

Medications

If secondary hypertension is ruled out, we suggest the use of, the triple combination of an angiotensin-converting

enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), a long-acting dihydropyridine calcium channel blocker (usually amlodipine), and a long-acting thiazide diuretic is often effective and generally well tolerated. Further, addition of spironolactone can augment the effect. The more specific aldosterone blocker, eplerenone, does not induce the side effects seen with spironolactone. Among patients with an estimated glomerular filtration rate of less than 30 thiazide diuretics are less effective, and loop diuretics, such as furosemide and torsemide may be necessary for effective volume control. Torsemide with its more predictable absorption and longer duration of action may be preferred.

If beta blockers are used, a vasodilating beta blocker, such as labetalol, carvedilol or nebivolol, may provide more antihypertensive benefit with fewer side effects compared to traditional beta blockers. Direct vasodilators hydralazine or minoxidil are reserved for patients who remain hypertensive despite the above approach.

Prognosis depends on the

- Degree and duration of resistant hypertension
- Extent of target organ damage
- Curable secondary causes

CONCLUSION

When a clinician encounters a patient with uncontrolled hypertension it is advisable to exclude the common cause like inadequate drug regimen, noncompliance, and unhealthy life style before arriving at a diagnosis of resistant hypertension. This diagnosis necessitates a detailed historical, clinical, and investigative analysis to search for the underlying cause and address the same, which will be rewarding.

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