



Review Article

Select Considerations for Secondary Hypertension

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Abstract

Hypertension assumes a dominant position among chronic non-communicable diseases worldwide. Of this, secondary hypertension constitutes only 5–10% of the total disease burden. In routine clinical practice, physicians come across hypertensive cases which are difficult to control despite optimal therapy. In this backdrop, the present paper reviews the less frequently encountered etiologies of hypertension which can pose difficulties to both the patient and treating clinician. This is classified as secondary hypertension and the major entities include renal parenchymal diseases, renovascular diseases, primary hyperaldosteronism, and sleep-disordered breathing. Among patients with resistant hypertension, investigations such as urine analysis, renal function tests, electrolytes, sonogram for kidneys, duplex ultrasound for renal artery stenosis, plasma aldosterone concentration/plasma renin activity (PAC/PRA) ratio, and sleep study may be done in serial manner depending on the individual patient to identify a secondary cause. Drug-induced high blood pressure should also be addressed, especially in young ladies due to oral contraceptives pills and in chronic obstructive pulmonary disease patients on long-term steroids. Many a time, a proper evaluation and diagnosis can reduce the pill burden and long-term consequences of resistant hypertension.

Key words: Endocrine, renovascular, secondary hypertension, sleep disorder

Introduction

Increasing prevalence of hypertension is a global epidemiological concern, as the disease already tops the burden of chronic diseases across the world. Indian scenario turns out to be more worrying due to several reasons; specifically, the growing size of the urban population and economic burdens leading to stressed lifestyles. Hypertension has been marked as the most common single diagnosis by the primary care providers.^[1-3] An overriding majority of these hypertension cases (90–95%) fall under essential or idiopathic hypertension category.

Secondary hypertension is the effect of a definite, identifiable predisposing cause and accounts for approximately 5–10% of cases. Secondary hypertension often goes underdiagnosed, leading to lifelong medications. End-organ damage is earlier and more prevalent due to the resistant nature of hypertension in these patients. This deems important, particularly in countries such as India, where the likelihood of obesity is increasing at an alarming rate due to change in lifestyle patterns, consumerism, and related factors.^[4-6] Unlike patients with primary or essential

hypertension those with secondary hypertension need extensive investigations, resulting in greater psychological distress and financial burden which leads to a vicious cycle of irregular follow-up and poor compliance. However, proper case selection, evaluation, and focused treatment strategies lead to complete or partial cure in good proportion of patients.^[7]

Evidence reveals an array of causes for secondary hypertension which broadly could be classified into renal, endocrine, cardiovascular/pulmonary, and drug induced. The present review makes an attempt to focus on, the major etiologies of secondary hypertension such as renovascular hypertension (RVHTN), endocrine hypertension due to primary hyperaldosteronism, and hypertension due to sleep-disordered breathing.

An Updated Overview of Management Protocols for Secondary Hypertension

Secondary hypertension is strongly suspected in the following situations:

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1. Persistent hypertension in spite of concurrent use of optimal doses of at least three antihypertensive drugs belonging to three different classes, of which one is a diuretic. This is termed as resistant hypertension.
2. Labile hypertension or acute rise in blood pressure in a person with previous optimal control.
3. Sudden onset of hypertension in persons with no family history or risk factors, who are <30 years of age and are non-obese or in patients more than 55 years of age.
4. Malignant or accelerated hypertension accompanying a target organ damage such as heart failure, acute kidney injury, retinal hemorrhage, papilledema, or neurological disturbances.
5. Hypertension with dyselectrolytemia – hypokalemia and metabolic alkalosis.
6. Well-documented age of onset before puberty.

Major Causes of Secondary Hypertension

Renal causes

- Renal parenchymal hypertension
- RVHTN.

Endocrine causes

Primary hyperaldosteronism

- Cushing's syndrome
- Pheochromocytoma
- Hypothyroidism
- Hyperparathyroidism.

Cardiovascular or cardiopulmonary causes

- Coarctation of aorta
- Obstructive sleep apnea (OSA).

Drugs

- Glucocorticoids, NSAIDs, combined oral contraceptive pills, calcineurin inhibitors, caffeine, phenyl ephedrine, and erythropoietin.
- Inherited rare causes such as Liddle's syndrome and Gordon's syndrome.

Renal parenchymal diseases

Primary renal disease is the most common cause of secondary hypertension and can happen in acute as well as chronic kidney disease (CKD). Hypertension is present in more than 80% of patients with CKD. Out of this, glomerular diseases cause more severe hypertension than tubulointerstitial diseases. Clues for diagnosis are the presence of proteinuria, especially more than 1000 mg/day, active urine sediment (with RBCs, WBCs, and casts) and other sonological and histological features favoring a renal pathology. On the other hand, long-standing uncontrolled blood pressure can also cause nephrosclerosis and then many a time, clinicians find it difficult to identify whether hypertension

or renal disease was the initial problem. The etiology of hypertension in CKD could be clinically discernible from the occurrence of one or more of such symptoms as extracellular volume overload, increased renin-angiotensin-aldosterone activity, endothelial cell dysfunction, oxidative stress, increased vasopressin release, and hypertensinogenic drugs such as erythropoietin and steroids.

Detailed evaluation of primary renal disease with appropriate tests (sonogram, urinalysis, histopathology, etc.) is required. Uncontrolled hypertension adds on to significant morbidity and mortality in CKD, across all stages, by causing rapid progression of renal failure and its associated huge cardiovascular risk. The target blood pressure recommends in patients with significant proteinuria (500–1000 mg/day) is 130/80 mmHg. Angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) are preferred agents in CKD, but periodic monitoring of creatinine and serum potassium is advised.^[8,9]

RVHTN

It caused by occlusive lesion of a renal artery resulting in reduction of renal artery perfusion pressure. It is most often a potentially curable cause of hypertension. RVHTN is relatively uncommon in patients with mild hypertension but quite common in patients with severe or refractory hypertension, especially in patients with other atherosclerotic diseases such as aortic disease, peripheral occlusive arterial disease, and coronary disease. Renal artery disease if progressive can cause decline in glomerular filtration rate (GFR) and such resultant CKD is called as ischemic nephropathy.^[7,10] Atherosclerosis affecting the renal artery, mostly at its origin accounts for 85% of cases. Fibromuscular dysplasia (FMD) which is a non-inflammatory, non-atherosclerotic disorder affecting young ladies is the second most common cause of RVHTN.^[11,12]

Table 1: Clinical features of renal artery stenosis due to atherosclerosis and fibromuscular dysplasia

Patient factor	ARAS	FMD
Prevalence	2/3	1/3
Age	15–50	>50 years
Sex	(More in) Males	(More in) Females
Renal failure	Common	Uncommon
Site	Ostium, first 1–2 cm of renal arteries	Distal part of main renal artery
Association	Other risk factors of atherosclerosis	Familial in 10%, carotid vertebral artery disease
Progression	Fast involving other arteries	Slow progression
Angiography	Bilateral in 20–40%, high-grade diffuse	String of beads appearance
Response to treatment	Case-to-case variation	Curative in 50% with angioplasty, if indicated

ARAS: Atherosclerotic renal artery stenosis, FMD: Fibromuscular dysplasia

Clinical characteristics of these two pathologies are detailed in Table 1.

Clinical Clues to RVHTN^[10,11]

- Late-onset severe hypertension – more than 180/120 blood pressure after the age of 55 years.
- Episodes of flash pulmonary edema with normal ventricular function.
- Unexplained acute kidney injury (AKI) within 1–2 weeks of starting ACEI or ARB.
- Asymmetric kidney size with more than 1.5 cm difference.
- Severe hypertension with features of diffuse atherosclerosis, especially in >50 years.
- Presence of unilateral systolic-diastolic bruit.

Establishing the Diagnosis of RVHTN

Detailed diagnostic testing is advocated only in those patients with high clinical suspicion and those who have high likelihood of benefiting from the procedure. Compelling indications for extensive evaluation include as follows:

- A short duration of accelerated hypertension
- Failure or intolerance to optimal medical therapy
- Progressive renal failure in the absence of another etiology for CKD
- High clinical suspicion of FMD in young hypertensives.
- Recurrent flash pulmonary edema.^[11,12]

The gold standard for diagnosing renal artery stenosis is renal arteriography. However, a variety of less invasive tests is available for initial evaluation. They are renal artery duplex ultrasonography (RADUS), CT angiography, and MR angiography. The choice of the test depends on patient factors and institutional expertise. Testing for RVHTN is associated with potential risks, particularly in patients with impaired renal function who are at risk for contrast-induced nephropathy and nephrogenic systemic fibrosis associated with gadolinium exposure during MR angiogram. Invasive testing is done if the screening tests are inconclusive with highly suggestive clinical setting.

RADUS is an important diagnostic test in assessing RAS. It is relatively easier non-invasive test which can be repeated and it provides functional assessment of the renal arteries along with certain anatomical information.

Peak systolic velocity 180 cm/s and/or a relative velocity above 3.5 as compared to the adjacent aortic flow are useful. This has a sensitivity and specificity of 90 and 96%, respectively, in lesions having more than 60% stenosis determined angiographically. As with many diagnostic procedures, a positive test is more informative than a negative test. Disadvantages of Doppler study of renal arteries in diagnosing RVHTN are its operator dependence, failure to identify accessory, distal branch stenosis, and inability to predict outcome after revascularization.^[13]

Spiral CT scan with CT angiography is highly accurate for atherosclerotic RAS but less useful for FMD.

Magnetic Resonance Angiography

It provides excellent vascular images of RAS, especially gadolinium contrast-enhanced images. The risk of nephrogenic systemic fibrosis is avoided by technical improvements in MRA like breath-hold MRA with paramagnetic less nephrotoxic contrast material.

Invasive imaging

Intra-arterial angiography is the gold standard for diagnosing RAS. More than 70% stenosis in angiography, resting translesional mean pressure gradient of more than 10 mmHg, and renal fractional flow reserve ≤ 0.8 are features to suggest a hemodynamically significant stenosis. However, most centers do not proceed directly to arteriography due to the risk of contrast nephropathy and cholesterol embolization. If there is huge suspicion of RVHTN both clinically and by way of screening tests like Doppler, CTA, or MRA, one can proceed with invasive arteriography. This is particularly useful in young FMD patients where non-invasive tests might miss the lesion.^[14,15]

Carbon dioxide angiography – CO₂ is useful as an alternative contrast agent either alone or in combination with smaller doses of iodinated contrast. It is the only known contrast agent which is non-nephrotoxic. CO₂ is also of help in people with hypersensitivity to iodine-containing contrast medium. It is worth mentioning here that though CO₂ is regarded as a useful contrast agent, it should not be used in coronary, cerebral, and thoracic imaging due to its potential neurotoxicity. Lack of familiarity restricts its use in day-to-day practice.^[15]

In patients without renal failure Doppler study, CT angiography and MR angiography are safe and useful tests before proceeding with intrarenal arteriography. However, in patients with renal failure, both invasive and non-invasive tests using contrast agents carry risk of nephrotoxicity. In patients with GFR <30 ml/mt, CT angiogram is preferred over MR angiogram due to higher risk of gadolinium-induced nephrogenic systemic fibrosis.

Treatment of Unilateral Renal Artery Stenosis – Three Options are Available^[16-20]

1. Medical management – Medical management should be essentially offered to all patients. Addition of ACE inhibitors and ARBs has markedly improved blood pressure control. If adequate blood pressure control is not achieved, diuretics, long-acting calcium channel blockers, beta-blockers, etc., may be added as in primary hypertension. Progressive stenosis resulting in long-term ischemic changes in the kidneys and resultant renal failure is potential concerns with medical management.
2. Revascularization by percutaneous transluminal renal angioplasty with stenting is advised in patients who have a high likelihood of benefiting from the procedure and in patients who fail to tolerate or achieve optimal

blood pressure control with medical management. This includes patients who have a short duration of refractory hypertension, young ladies on multiple drugs in whom the chances of FMD are high and in those with refractory heart failure with resistant hypertension and repeated occurrence of flash pulmonary edema. Observational outcome studies of atherosclerotic renal artery stenosis from 14 series of trials comprising 678 patients showed hypertension cure defined as BP <140/90 with no antihypertensive medications were seen in 12%. In 73% BP level improved with lesser number of drugs and in 41%, the renal function also improved. Proper selection of patient who is best suited for this treatment is important rather than performing angioplasty in all innocent incidental lesions.

3. Surgical treatment – Splenorenal and hepatorenal bypass surgeries are less commonly performed in selected category of patients with complex anatomical lesions and with severe aortoiliac occlusive disease.

Treatment of Bilateral Renal Artery Stenosis

All management options discussed with unilateral renal artery stenosis are applicable in the case of bilateral disease also. Additional concerns here are high chances of chronic ischemic nephropathy, progressive renal failure, and hemodynamically mediated AKI while on ARB or ACE inhibitors.

Endocrine Hypertension

Primary hyperaldosteronism^[21-23]

It is the most common but often underdiagnosed cause of hypertension due to an endocrinopathy. Among patients with resistant hypertension, the prevalence is around 11–20%. It may be caused by bilateral adrenal hyperplasia (65% of cases), aldosterone-producing adenoma (30%), or rarely secretory adrenal carcinoma or inherited endocrinopathies. Other than features of resistant hypertension, patients can present with episodic paralysis secondary to hypokalemia and alkalosis.

Screening for hyperaldosteronism is recommended for the following groups:

1. Sustained BP >150/100 on three different occasions, resistant hypertension despite three drugs, or controlled hypertension on four or more drugs.
2. Hypertension with spontaneous or diuretic-induced hypokalemia.
3. Hypertension with adrenal incidentaloma.
4. Hypertension with OSA.
5. Hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age of <40 years.
6. All hypertensive first-degree relatives of patients with PA.

Measurement of the ratio of plasma aldosterone concentration (PAC) to plasma renin activity (PRA) is the screening test of choice. Although at present, there are no firm recommendations for aldosterone to renin ratio cutoffs, due to

variability of assays, a PAC/PRA >20 in combination with a PAC >15 ng/dl or 416 pmol/L is considered as a positive screening test result. Many factors such as GFR, diet, drugs, potassium level, and menstruation etc affect the value and hence should be appropriately addressed before screening.

How to Confirm?

The hallmark of primary aldosteronism is non-suppressible aldosterone secretion with non-stimulable renin secretion. Therefore, aldosterone suppression tests with fludrocortisone, saline suppression test, and oral salt loading are suggested. Since their tests are cumbersome, time consuming, and with risks attached, radiological methods are preferred. CT and MRI are used to differentiate between a unilateral and bilateral adenoma. Adrenal vein renin sampling is theoretically useful but difficult to put in practice.

Treatment

Medical management is best with aldosterone antagonists such as eplerenone, spironolactone, or amiloride. Additional antihypertensives like ARBs are most often needed. Surgical removal and ethanol embolization are done for unilateral adenomas. If no discrete nodules are identified in the CT scan with negative adrenal vein renin lateralization, it is advisable to do follow-up under medical management.

Sleep Apnea Syndrome

Sleep apnea syndrome has emerged as an independent risk factor for hypertension irrespective of the associated metabolic factors such as diabetes, dyslipidemia, and obesity. Around 50% of patients with OSA are estimated to be having hypertension. Although OSA has been linked to high risk for cardiovascular disease, stroke, pulmonary hypertension, and arrhythmias, the association with hypertension is very much obvious in all longitudinal and cross-sectional studies. The observed risk factors are male sex, ethnicity, and high apnea-hypopnea index (more than 30/h). Increased sympathetic nervous system activity and abnormal vascular functional and structural changes resulting from oxidant stress are supposed to be contributory factors for hypertension. Sleep study is diagnostic. Weight reduction and continuous positive airway pressure are beneficial in most of the patients and surgical intervention is rarely needed.^[24,25]

Conclusion

Secondary hypertension being rare often goes underdiagnosed. It is not cost effective to evaluate extensively every hypertensive person for a secondary cause. Young hypertensives, those who develop early target organ damage and patients on multiple drugs, should be screened for a treatable cause, in these patients if investigations are carefully selected, it is an extremely fruitful exercise because in a good proportion of patients, hypertension can either be cured or at least better controlled. The common

causes of secondary hypertension are renal parenchymal diseases, renovascular diseases, primary hyperaldosteronism, and sleep-disordered breathing. Among patients with resistant hypertension, investigations such as urine analysis, renal function tests, electrolytes, sonogram for kidneys, duplex Doppler ultrasound for renal artery stenosis, PAC/PRA ratio, and sleep study can be done serially to rule out a secondary cause. Drug-induced hypertension should always be addressed in young ladies on oral contraceptives pills and in chronic obstructive pulmonary disease patients on long-term steroids. Rarer causes include pheochromocytoma, Cushing's syndrome, and coarctation of aorta which should be excluded in appropriate clinical settings. With the background of fast-growing economy, unhealthy lifestyle practices, and progressive urbanization, we have a growing epidemic of obesity and metabolic syndrome and therefore of OSA. More studies should be directed to identify hypertension in relation to OSA and sleep-disordered breathing.

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