

Review Article

Rare and unusual causes of hypertension

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Abstract

Background: Hypertension in most cases is primary, the exact etiology not known but there may be risk factors such as salt excess, obesity, lack of physical activity, genetic factors, metabolic syndrome, and diabetes. However, there exists a subgroup of patients with hypertension with underlying etiology, referred to as secondary hypertension, and constitutes about 5–10% of patients with hypertension. The importance of diagnosis of the secondary causes of hypertension is to detect a potentially reversible etiology. Some of these causes are rare and unless looked for, can be easily missed.

Methods: A review of age-specific causes, approach, rare diseases of the aorta, endocrine, renal, iatrogenic, and substance abuse have been discussed. The importance of suspecting unusual causes in patients with uncontrolled hypertension, hypertension in the young, in the presence of target organ damage is emphasized. Case reports of rare cases have been included.

Conclusion: A systematic approach and knowledge of various rare causes will help suspect and lead to the correct diagnosis in many cases of secondary rare causes of hypertension. It gives a unique opportunity to cure hypertension in some cases and if the underlying cause is undiagnosed may result in morbidity and even prove fatal in some cases.

Key words: Secondary hypertension, renal artery stenosis, coarctation of aorta, pheochromocytoma, pseudopheochromocytoma, hyperaldosteronism

Introduction

Hypertension in >90% of cases is primary hypertension with the interaction between genetic and multiple environmental cardiovascular risk factors. Some of the underlying etiologies of hypertension are rare and may go undiagnosed unless a systematic approach and targeted testing are done. Many secondary causes are underlying etiology of resistant hypertension and passed off as essential hypertension in the absence of a careful clinical and diagnostic evaluation.^[1]

Clinical Examination

A thorough clinical examination may give some pointers to secondary hypertension. Some clinical findings which may be helpful to detect the secondary causes of hypertension include presence of radio femoral delay suggests coarctation of aorta. Differences in limb blood pressure, the presence of vascular bruit - may unveil coarctation of aorta, Takayasu's arteritis

or Peripheral vascular disease which may be associated with atherosclerotic renal artery stenosis (RAS).

An abdominal bruit is often present in RAS, especially in fibromuscular dysplasia in young postural hypotension - 40% of cases of the pheochromocytoma are associated with postural hypotension, paroxysmal hypertension is common in pheochromocytoma, pseudopheochromocytoma, and panic disorder.

Clinical features of hyper or hypothyroidism, cushingoid features may be suggestive of underlying endocrine disorder obesity, excess snoring with day time somnolence is suggestive of obstructive sleep apnea (OSA).

Diagnostic approach

An age-specific approach is recommended

In patients in early childhood, secondary causes are underlying in 70–85% of cases.^[2] The most common causes are renal causes. Reflux

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uropathy is common in young boys. In adults >18 years, renal causes and coarctation of aorta are the common secondary causes in about 10–15% of cases of the hypertension. In young adults, RAS due to fibromuscular dysplasia should be considered along with coarctation of the aorta and other renal causes. In the middle-aged, renal causes, thyroid disorders, OSA, and primary hyperaldosteronism are some of the secondary causes, whereas in the elderly renal causes and atherosclerotic RAS are important to be considered [Table 1].

Investigations

The basic investigations include:

- Blood sugar
 - Lipid profile
 - Blood urea, serum creatinine, serum electrolytes, and serum calcium
 - ECG
 - X-ray chest
 - ECHO
 - Ultrasound abdomen
 - Renal Doppler
 - Thyroid function test
 - Urinary 24 h metanephrine, plasma metanephrine
 - Plasma aldosterone/renin ratio
 - Serum cortisol
 - Polysomnography
 - Computer tomography (CT)/Magnetic resonance imaging (MRI)/CT or MRI angiogram/metaiodobenzylguanidine (MIBG) scan in special situations
 - Invasive angiogram, usually when planned for intervention
- Evaluation for secondary causes is recommended in the following situations^[3]
1. Hypertension in age <40 years > Grade 2, and no genetic or overt risk factors, and hypertension in childhood
 2. Severe hypertension and hypertensive emergencies

3. Hypertension with target organ damage
4. Lack of control in previously well-controlled hypertensive
5. Evidence of abnormal renal function, electrolytes, or abnormal endocrine tests.
6. Presence of bruit, murmur, absent pulses, and variation in blood pressure in the limbs.
7. Paroxysmal hypertension.
8. Clinical features of OSA.
9. Deterioration of renal function on the initiation of angiotensin-converting enzyme inhibitors (ACEI) or ARB drugs.

Secondary causes of hypertension

Renal causes

Two major types of renal diseases - renal parenchymal disease or RAS cause secondary hypertension. Renal parenchymal diseases include glomerulonephritis, polycystic kidney disease, diabetic kidney disease, and chronic pyelonephritis. Reflux uropathy is an important cause in pediatric age group boys. RAS in younger individuals is usually due fibromuscular dysplasia which response very well to interventional therapy. It can also be secondary to Takayasu’s arteritis. In older adults, it is usually atherosclerotic in origin. Renal angioplasty has doubtful benefits in atherosclerotic long-standing RAS. It is reserved for patients with uncontrolled hypertension, flash pulmonary edema, bilateral RAS, or sudden deterioration in renal function. Whenever there is a deterioration of renal function following use of ACEI or ARB’s, it is important to look for RAS. RAS can be diagnosed by renal Doppler, CT, or MRI angiogram. In individuals with raised serum creatinine noncontrast, MRI angiogram can be done.

Disorders of aorta

Coarctation of aorta is the second most common etiology of secondary hypertension next only to renal causes in pediatric and

Table 1: Age-based diagnostic approach of secondary hypertension

Age group	Common etiology	Initial investigations	Percent of hypertensive patients with secondary cause (%)
<12 years	Renal causes	Urine analysis	70–85
	Reflux uropathy	Renal function test	
	COA	Usg abdomen	
12–18 years	Renal causes	Urine analysis	10–15
	COA	Renal function test	
		USG Abdomen	
		ECHO	
Young adults 19–40 years	Renal parenchymal diseases	Renal function tests	5–10
	RAS-Fibro muscular dysplasia	Renal doppler	
	COA	ECHO	
Middle-aged - 40–65 years	Primary aldosteronism	Aldosterone/renin ratio	5–15
	Renal parenchymal disease	Polysomnography	
	OSA	Thyroid function tests	
	Thyroid disorders		
Old age >65 years	Renal parenchymal disease	Renal function test	5–10
	RAS-Atherosclerotic	Renal Doppler	
	Thyroid disorders	CT/MRI Renal angiogram	
		Thyroid function test	

young adults. The most important sign is a radio-femoral delay and difference in pressure between the limbs. It can be diagnosed by ECHO, MRI angiography, or CT aortogram. Council of Architecture (COA) patients benefit from aortoplasty and stenting or surgical repair. The usual lifespan of uncorrected COA is about 50 years with complications due to hypertension, dissection, or heart failure.

We had a 65-year-old patient detected to have coarctation during evaluation of severe bicuspid aortic stenosis who underwent successful coarctation angioplasty and stenting.

Takayasu's arteritis is rare non-specific arteritis involving aorta and its branches. It is a chronic granulomatous arteritis involving large muscular arteries and results in areas of stenosis, occlusion, dilatation, and aneurysms. The disease occurs in young women predominantly in the second or third decades and is associated with hypertension in two-thirds of patients. Absent upper limb pulses, subclavian bruit, and high blood pressure more often in lower limbs are present, hence called "reversed coarctation." The cause of hypertension in Takayasu's disease may be RAS, atypical coarctation or diffuse aortic narrowing. Renal angioplasty or aortic angioplasty can be done in Takayasu's arteritis as well, but they are more hard and fibrotic lesions and generally need higher inflation pressures or cutting balloon angioplasty. The reported success is about 85–90% with an incidence of restenosis in about 15–20% [Figure 1].^[4]

We had a 45-year-old female with Grade 2 hypertension with left renal artery total occlusion, right renal artery 80% stenosis, diffuse aortic narrowing, and aneurysmal dilatation of right iliac artery. She underwent percutaneous transluminal renal angioplasty (PTRA) of the right renal artery.

Autoimmune arteritis like polyarteritis nodosa (PAN) can involve renal arteries. PAN is often associated with hepatitis B infection in close to 10% of cases. PAN may be associated with renal artery aneurysms and stenosis combined. PAN needs immunological treatment, renal angioplasty, and hepatitis treatment combined in these cases [Figure 2].

Endocrine causes

The most common endocrine cause is a hyperaldosteronism. Hyperaldosteronism can be due to unilateral macroadenoma or bilateral diffuse adrenal hyperplasia. It is more common in middle-aged adult men between 40 and 65 years. Unprovoked hypokalemia, though suggestive is present only in 30% of the cases. Diuretic-induced hypokalemia or low normal $K^+ < 3.9$ in the presence of ACEI/ARB therapy should also lead to suspect and evaluate for hyperaldosteronism. Any case of resistant hypertension should have an evaluation for primary hyperaldosteronism. It is diagnosed by doing a plasma aldosterone/renin ratio after correcting hypokalemia and patients should not be on aldosterone antagonist therapy. CCB, hydralazine, and prazosin can be used for hypertension control without interfering with the test. Aldosterone/renin ratio > 20 ng/dl with aldosterone level > 15 ng/dl is suggestive of the diagnosis.^[5]

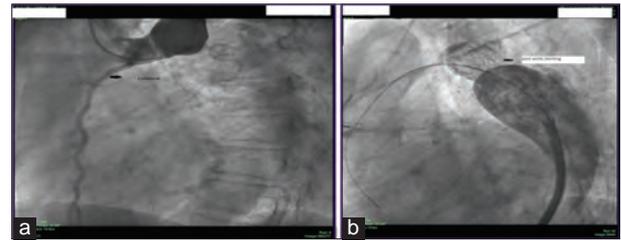


Figure 1: Aortogram of council of architecture, (a) diagnostic, (b) post stenting

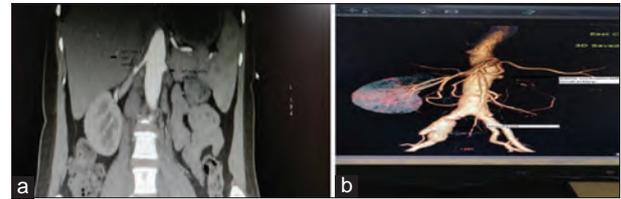


Figure 2: (a) Computer tomography abdominal aortogram, (b) Diagnostic renal angiogram-renal angiogram post percutaneous transluminal renal angioplasty of right renal artery

The treatment is surgical for macroadenoma and use of aldosterone antagonists for microadenoma.

We had a 65-year-old gentleman with Grade 3 hypertension, hypokalemia of 1.9, elevated aldosterone and suppressed renin levels, CT imaging failed to detect a tumor, a diagnosis of microadenoma was made, treatment started with aldosterone antagonist spironolactone 25 mg and losartan 50 mg and he responded well to treatment with correction of hypokalemia and blood pressure control and doing well on > 15 years follow-up.

Hyperaldosteronism can also be familial. There are four types described. Type 1 is an autosomal dominant condition, glucocorticoid-responsive disorder, associated with severe hypertension, young age, and family history. Hypokalemia is less common and cerebrovascular complications and rupture of intracranial aneurysms are common. The treatment is low dose steroids in the night to suppress ACTH surge in the morning along with mineralocorticoid receptor antagonists.^[6]

Type 2 is a chromosomal defect, bilateral and clinically similar to sporadic type, type 3 is due to a potassium channel defect, and type 4 is due to calcium channel defect.

Gordon's syndrome: It is a rare monogenic disorder affecting NA-CL cotransporter in the distal renal tubule. It is associated with short stature, mental retardation, dental abnormalities, severe hypertension, hyperkalemia, hyperchloremia, and metabolic acidosis.

It responds to thiazide diuretics. It is also called as pseudohypoaldosteronism, it is associated with normal aldosterone and renin levels.^[7]

Geller syndrome is a rare autosomal dominant disorder with hypertension exacerbated in pregnancy due to abnormalities of mineralocorticoid receptor interaction with progesterone.^[8]

Congenital beta- or alpha-hydroxylase deficiency and glucocorticoid-resistant hyperaldosteronism (Chrousos

syndrome) - ACTH overactivity with the resistance of the glucocorticoid receptor, are some of the rare congenital defects associated with secondary hypertension.

Thyroid disorders

Both hypothyroidism and thyrotoxicosis can be associated with hypertension. Hypothyroidism causes diastolic hypertension; thyrotoxicosis causes systolic hypertension.

Hyperparathyroidism

Hyperparathyroidism causes secondary hypertension, hypercalcemia, vascular calcification, bone pains, and renal calculus.

Cushing's syndrome

It is usually due to steroid use but can be due to adrenal tumors or ACTH producing pituitary tumors, usually diagnosed by the presence of cushingoid features, striae, and purpura. Evaluation is by measurement of 24 h cortisol levels.

Pheochromocytoma

It is a rare cause - 0.5% of secondary hypertension, suspected by the presence of flushing, sweating, palpitation, headache, and labile hypertension. Use of beta-blockers, tricyclic antidepressants, and metoclopramide, and sympathomimetic drugs can precipitate hypertensive surges. It is a catecholamine-secreting tumor from adrenal medulla or extra-adrenal sympathetic ganglia. The adrenal tumor can be a unilateral macroadenoma or bilateral diffuse adrenal hyperplasia. 40% of pheochromocytoma is familial, which is more often bilateral or extra-adrenal. Pheochromocytoma is present in 50% of patients with multiple endocrine neoplasia type 2, 10–20% of patients with Von Hippel-Lindau syndrome, and 0.1–5% of patients with neurofibromatosis.^[9]

6 P's characteristic of pheochromocytoma is as follows:

1. Paroxysmal hypertension
2. Palpitation
3. Perspiration
4. Postural hypotension
5. Pounding headache
6. Pallor

It is diagnosed by measurement of 24 h urinary metanephrines or plasma free metanephrines. Ultrasound may not be able to delineate the tumors well. CT or MRI imaging is required for detection of tumor masses, MIBG scan is used to diagnose extra-adrenal paragangliomas. 10% of pheochromocytoma is malignant with renal or bone metastases. Delayed recurrence can occur after several years; hence, periodic surveillance is recommended. Surgical removal of a tumor can cure hypertension. Adequate alpha-blockade by the use of phenoxybenzamine or prazosin followed by beta-blockade is essential before surgery. Calcium channel blockers only can be used in mild cases and metyrosine in severe cases [Figure 3].

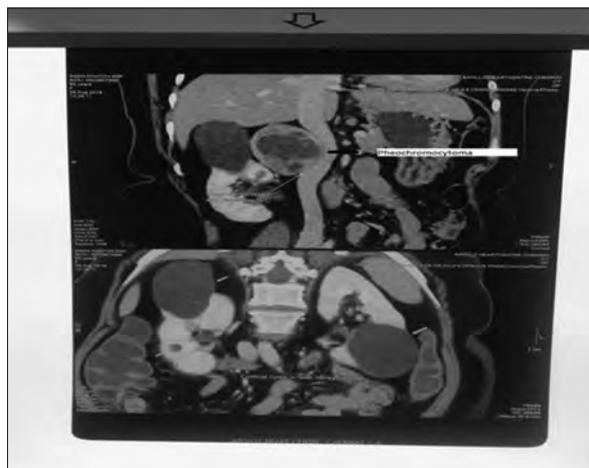


Figure 3: Computer tomography imaging of a case of pheochromocytoma

Pseudopheochromocytoma

Pseudopheochromocytoma is a cause of paroxysmal hypertension caused by catecholamine excess, mimics pheochromocytoma but does not have the biochemical or imaging features of pheochromocytoma. Pseudopheochromocytoma is more common in women, and the acute elevated blood pressure is accompanied by chest pain, nausea, dizziness, palpitation, and lasts for few minutes to several hours. It differs from panic attack as there is no definite anxiety or fear preceding the episode, though childhood trauma or underlying psychosocial stresses have been found in many cases. These patients respond to clonidine and clonazepam. Anxiety and psychosocial counseling help in prevention of the paroxysms.^[10]

Liddle's syndrome

It causes hypokalemia but is associated with normal or low aldosterone and low renin levels. It is due to an autosomal dominant condition resulting in overactivity of the epithelial sodium channel in the luminal side of collecting tubule of kidney leading to sodium retention, hypokalemia, metabolic alkalosis, and hypertension. It is diagnosed by the presence of hypokalemia with low renin and aldosterone levels and increased urinary sodium levels. This hypertension responds to amiloride or triamterene, and mutual recognition agreement drugs have no role in this condition. A case of known Liddle's syndrome successfully managed during pregnancy with amiloride has been reported.^[11]

Reninoma

It is a rare benign renin-producing juxtaglomerular tumor produces renin, causes secondary hyperaldosteronism with hypokalemia and metabolic alkalosis and hypertension and it responds to RAS inhibitors, and the definitive treatment is surgical removal. The diagnosis is suspected due to headache with severe hypertension, hypokalemia with metabolic alkalosis, usually in young adults,

investigations show high renin and aldosterone levels and the tumor is detected by imaging by CT or MRI. Excess renin by renin vein sampling can be used for lateralization of the tumor.^[12]

Acromegaly

Excess growth hormone can produce hypertension.

Sleep-apnea

It is a common cause of resistant hypertension in obese older adults. It is diagnosed by polysomnography. It is cost-effective to initially screen using sleep apnea scale and nighttime pulse oximetry. Weight reduction and continuous positive airway pressure therapy in moderate-to-severe sleep apnea can help controlling secondary hypertension.

Iatrogenic

Drugs causing hypertension include

- NSAIDs are one of the common drugs causing hypertension
- Steroid therapy for autoimmune, skin diseases
- Oral contraceptive pill with estrogen can cause usually mild, but rarely severe hypertension
- Nasal decongestants-phenylephrine
- Liquorice - can stimulate mineralocorticoid receptor causing hyperaldosteronism
- Cancer chemotherapy agents - antiangiogenic drugs - VEGF inhibitors such as bevacizumab, and tyrosine kinase inhibitors such as sunitinib and sorafenib
- Immunosuppressant like cyclosporine.
- Erythropoietin
- Vitamins and herbal drugs such as ginseng, ephedra, and mahuang.

Substance abuse

Alcohol is one of the most commonly abused agents causing hypertension. Alcohol causes hypertension through multiple mechanisms. Increased sympathetic activity, cortisol release, endothelial injury, and activation of renin-angiotensin system, activation of endothelin, loss of endothelial nitric oxide release, and activation of calcium channels have been proposed.

The treatment is cessation or reduction in alcohol use, ACEI/ARB, and calcium channel blockers.^[13] Cocaine, methamphetamine is some of the other agents causing hypertension.

Miscellaneous

ACTH producing lung tumors, brain neoplasms can cause hypertension.

Carcinoid syndrome can cause flushing with hypertension.

Guillain-Barre syndrome, tetraplegia due to autoimmune and loss of CNS control respectively can cause neurogenic hypertension.

Conclusion

Secondary hypertension needs an age-based approach in the evaluation. An awareness of common and rare disorders is required to make the correct diagnosis. A careful history of symptoms, family history of rare disorders, a careful clinical examination, and judicious use of diagnostic tests can unravel the underlying cause in many patients and help to decrease the incidence of a missed diagnosis.

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