MEDIBEATS
The Medical Bulletin

In Nephrology

The prevalence of renovascular hypertension (RVH) may be as high as 10 - 40 % in patients with acute, severe, or refractory hypertension. though it accounts for only 1% to 2% of all cases of hypertension in the general population

Essential hypertension which occurs above 50 years, hypertension occurring below 50 years is thought to be secondary hypertension. Differential diagnosis of secondary hypertension is shown in the table 1. Renovascular hypertension is an important cause of secondary hypertension.

Renovascular Hypertension

RVH is due to presence of renal artery stenosis (RAS) which leads to increased renin production from ischemic kidney. However, the presence of RAS alone is not synonymous with renovascular hypertension. RAS may be an incidental finding and may not be functionally significant to cause hypertension. A functionally significant stenosis is characterised by pressure drop of 10-20 mmHg across the stenosis. Renovascular hypertension due to functionally significant RAS is characterised by

- Unexplained creatinine elevation and/or acute and persistent elevation of creatinine of at least 50% after administration of ACE inhibitor, ARB, or renin inhibitor
- Moderate to severe HT in a patient with diffuse atherosclerosis
- Asymmetry in kidney size of more than 1.5 cm
- Moderate to severe hypertension in patients with recurrent episodes of flash pulmonary edema
- Onset of hypertension with blood pressure >160/100 mmHg after age 55 years
- Systolic or diastolic abdominal bruit (not very sensitive)

Etiology of Renovascular Hypertension

The chief causes of renovascular hypertension include fibromuscular dysplasia, Takayasu's arteritis and atherosclerotic renal disease. Other causes are mentioned in the Table 2.

Fibromuscular Dysplasia- It is an important cause of renal artery stenosis in the younger age group i.e., <45 years and is unilateral in 2/3rd of the cases. FMD affects the distal portion of the renal artery sparing the ostium and leads to arterial stenosis, occlusion, aneurysm, dissection, and arterial tortuosity. The most frequently involved arteries are the renal and internal carotid arteries, followed by the vertebral, visceral, and external iliac arteries.

When to suspect?

FMD should be suspected in young hypertensives who present with headache, cerebral hemorrhage, strokes, etc. Renal bruits can point to renovascular hypertension. Duplex doppler shows renal artery stenosis and angiography may show string of beads appearance. (Fig 1)

Takayasu's arteritis

The diagnosis of Takayasu arteritis depends on the clinical criteria. It is an inflammatory arteritis hence ESR, CRP are elevated. As per the ACR criteria patients are said to have TAK if 3 out of 6 criteria are present

- Age at disease onset ≤40 years
- Claudication of the extremities
- Decreased pulsation of one or both brachial arteries
- Difference of at least 10 mmHg in systolic blood pressure between the arms
- Bruit over one or both subclavian arteries or the abdominal aorta
- Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or other causes. (Fig 2)

There are 3 stages of Takayasu arteritis- (i) active where there may be fever, systemic symptoms, tenderness of vessels and high ESR and (II) chronic which is associated with fibrosis of vessels, absence of tenderness and normal ESR. TA is often thought to be associated with Tuberculosis.

It is an important cause of renovascular hypertension in India. Clinical clues are asymmetrical pulses and peripheral bruits. Collaterals may be seen on the back. Angiography shows narrowing of aorta or its branches with thickened vessel walls.

Atherosclerotic renal artery stenosis (ARAS)

In older age group i.e., > 45 years, atherosclerotic renal disease is the most common cause of reno vascular hypertension and affects the renal artery at the ostium. (Fig 3) These lesions are linked to atherosclerotic risk factors, including tobacco use, dyslipidemias, diabetes, and hypertension. It may present with unexplained progressive kidney failure, bland urine sediment with few cells or casts or mild to moderate proteinuria and unilateral or bilateral small kidneys. ARAS is associated with the presence of large vessel occlusive disease in 75 % of cases. ARAS may lead to progressive loss of GFR which is called ischemic nephropathy.

Symptoms

The hypertension is usually severe. It may present with hypertensive emergency or urgency. Flash pulmonary oedema can occur. Bilateral renal artery stenosis may present with pulmonary oedema and acute left ventricular failure. Hypertension is often resistant to treatment. The use of ACEI or ARBs may cause worsening of renal function.

Renal bruit may be observed in about 30%. A systolic-diastolic bruit is suggestive of significant renal stenosis. Bruit is heard with the bell of stethoscope 1.5" above and lateral to the umbilicus. Other sites are the in the lumbar region, in the renal angles as well. Peripheral pulses may be asymmetric in case of Takayasu's arteritis. Carotid pulses must be auscultated for presence of bruit. Chronic activation of the RAAS is implicated in the development of abnormal left-ventricular remodelling leading to cardiac dysfunction. prolonged reduction of blood flow with tissue hypoxia produces irreversible kidney damage and fibrosis, often designated "ischemic nephropathy".

Lab Tests

Urine examination is bland. Red blood cells may be seen in case of accelerated hypertension.

Serum creatinine and blood urea may be high in cases of bilateral renal artery stenosis.

Hypokalemia is generally observed due to increased renin and consequent increase in aldosterone secretion.

There is no sufficiently accurate, noninvasive radiologic or serologic diagnostic test that, if negative, will completely exclude the presence of renal artery stenosis. Non- invasive tests are done first. Commonly employed non-invasive tests are doppler ultrasound and captopril renogram (Figure 4). Doppler USG helps in diagnosis and assessment of severity of RAS. DTPA renogram helps in determination of differential renal function. Tests like renin activity, IVU are obsolete. CT angiogram and MR angiogram are very sensitive for detection of ARAS. All tests with their advantages and drawbacks are mentioned in Tables 3a and 3b

Invasive tests include Conventional angiogram. Pressure gradients across stenosis help in estimating severity. Though angiography is the gold standard for diagnosis of RAS, 2017 ACC/AHA hypertension guidelines state that testing for renal artery stenosis by angiogram is indicated if a corrective procedure (revascularization) would be performed if clinically significant renovascular disease were detected.

Diagnosis of renal artery stenosis in patients with renal insufficiency

Those with bilateral atherosclerotic renal artery disease may often have renal insufficiency. Disparity in renal size is often not evident as disease is bilateral. Renal artery stenosis may be suspected due to worsening renal function or uncontrolled hypertension or any other arterial disease i.e., coronary artery disease. Contrast agents are contraindicated. Doppler is the investigation of choice. DTPA renogram is less sensitive. If inconclusive, CTA can be done with precautions to avoid contrast nephropathy. MRA is better avoided.

Treatment

Medical management

Management of Hypertension

BP GOAL-Though data from SPRINT and ACCORD recommend lowering BP to 120/80 mmHg, most guidelines recommend a blood pressure of 130/80mm Hg.

Drugs -Anti hypertensive agents are used for management of hypertension.

Hypertensive emergency is managed in the hospital setting with parenteral drugs like NTG, Nitroprusside, labetalol. Use of ACE/ARB therapy for patients with atherosclerotic disease indicate a mortality benefit. These are used for management of hypertension due to unilateral renal artery stenosis and are the drugs of choice. Though these drugs were traditionally contraindicated in bilateral renal artery stenoses, recent data demonstrates that they can be used even in bilateral RAS albeit cautiously. Other drugs like Calcium channel blockers, beta-blockers, alpha blockers can be used as required in combination.

Statins- ARAS patients should routinely be treated with statin therapy and lifestyle measures including withholding tobacco products.

Immunosuppressive agents-Steroids are used in acute stage of Takayasu arteritis. Other drugs used in steroid resistant disease include Azathioprine, Mycophenolate mofetil, Leflunomide, Methotrexate. Biologics include Infliximab, Etanercept, Tocilizumab etc.

Revascularisation

Revascularisation includes Renal angioplasty with or without stenting (drug eluting stents are also available) or a bypass graft.

Indications for revascularization are shown in table 4.

Re-vascularization is beneficial if the hypertension is of short duration.

- In atherosclerotic RAS, various trials have failed to show benefit with renal artery revascularization compared with medical treatment, in terms of either patient survival, cardiovascular events, or blood pressure.
- In FMD, revascularization is the mainstay of therapy. The options for revascularization in FMD include percutaneous transluminal angioplasty (PTA). PTA achieves similar technical success and is associated with a lower risk of adverse events. If PTA is not successful, or if a dissection occurs, stent implantation should be considered. The two main indications for open surgery include children with focal FMD (usually intimal fibroplasia) and if FMD is associated with renal artery aneurysm(s)

Role of nephrectomy

Rarely nephrectomy is done to remove the kidney producing renin and causing hypertension.

Differential diagnosis

RVH must always be considered in any patient with difficult to control hypertension. The diagnosis can be made on clinical grounds and can be confirmed with appropriate investigations. (Table1)

Conclusions

RVH is an important cause of resistant hypertension. Presence of renal bruit, asymmetric renal sizes, absence of peripheral pulse may point to stenosis in the renal artery. Fibromuscular dysplasia, Takayasu's arteritis and Atherosclerotic renal artery stenosis are common causes of RVH. Colour doppler of renal arteries and angiogram are important for diagnosis. Fibromuscular dysplasia is generally treated with angioplasty while atherosclerotic renal artery stenosis is treated medically with renin angiotensin system blockade though revascularization can be done if renal function deteriorates or there is pulmonary oedema. Diagnosing RVH is essential as it is a treatable cause of resistant hypertension.

Conclusion:

Renovascular hypertension is an important cause of resistant hypertension. Presence of renal bruit, asymmetric renal sizes, absence of peripheral pulse may point to stenosis in the renal artery. Fibromuscular dysplasia, Takayasu's arteritis and Atherosclerotic renal artery stenosis are common causes of renovascular hypertension. Colour doppler of renal arteries and angiogram are important for diagnosis. Fibromuscular dysplasia is generally treated with angioplasty while atherosclerotic renal artery stenosis is treated medically with renin angiotensin system blockade though revascularization can be done if renal function deteriorates or there is pulmonary oedema. Diagnosing renovascular hypertension is essential as it is a treatable cause of resistant hypertension.

Table 1	
Renovascular disease	• Renal bruits, asymmetric renal size, elevated renin • Colour doppler- parvus et tardus pattern, angiogram confirmatory
Primary kidney disease	• Elevated serum creatinine concentration • Abnormal urinalysis
Drug-induced hypertension:	• Oral contraceptives, Anabolic steroids, NSAIDs, Chemotherapeutic agents (eg, tyrosine kinase inhibitors/VEGF blockade) Stimulants (eg, cocaine, methylphenidate), Calcineurin inhibitors (eg, cyclosporine) • Antidepressants (eg, venlafaxine)
Pheochromocytoma	• Paroxysmal elevations in blood pressure • Triad of headache (usually pounding), palpitations, and sweating • Elevated urine and plasma metanephrines
Primary aldosteronism	• Unexplained hypokalemia with urinary potassium wasting; • however, more than one-half of patients are normokalemic • high aldosterone to renin ratio
Cushing's syndrome	• Cushingoid facies, central obesity, proximal muscle weakness, ecchymoses • May have a history of glucocorticoid use • High morning cortisol
Sleep apnea syndrome	• Common in patients with resistant hypertension, particularly if overweight or obese • Loud snoring or witnessed apneic episodes • Daytime somnolence, fatigue, and morning confusion
Coarctation of the aorta	• Hypertension in the arms with diminished or delayed femoral pulses and low or unobtainable blood pressures in the legs • Left brachial pulse is diminished and equal to the femoral pulse if origin of the left subclavian artery is distal to the coarct
Hypothyroidism	• Symptoms of hypothyroidism • Elevated serum thyroid stimulating hormone
Primary hyperparathyroidism	• Elevated serum calcium, high PTH

Table 2: Causes of renovascular hypertension

- Atherosclerotic renal artery stenosis
- Fibromuscular disease
  - Medial fibroplasia
  - Perimedial fibroplasia
  - Intimal fibroplasia
  - Medial hyperplasia
- Extrinsic fibrous band
- Renal trauma
- Arterial dissection
- Segmental renal infarction
- Page kidney (perirenal fibrosis)
- Aortic dissection
- Arterial embolus
- Aortic endograft occluding the renal artery
- Miscellaneous:
  - Hypercoagulable state with renal infarction (e.g., Lupus anticoagulant)
  - Autoimmune diseases (e.g., Takayasu's arteritis, Polyarteritis nodosa))
  - Malignancy encircling the renal artery (e.g., Renal cell carcinoma, pheochromocytoma)

Table 3a – Diagnostic tests for Renal artery stenosis			
	Diagnostic findings	**Advantages**	**Drawbacks**
Ultrasound	-Asymmetry of renal size Normal - left kidney is longer than the right by about 1.5 cm -Sizes outside range abnormal	-No radiation -Can be repeated	Not sensitive or specific
Doppler	-Velocity of blood at stenosis >150 cm/sec - delayed systolic peak - parvus et tardus pattern - resistivity index (peak systolic velocity - end-diastolic velocity /peak systolic velocity) is high (normal <0.7) Aortic renal gradient >3.5 Acceleration Time > 70ms.	No radiation exposure Can be repeated multiple times a positive test is more valuable than a negative one can be done in those with impaired renal function	sensitivity and specificity of doppler varies between 80-90%. Doppler is operator dependent time consuming.
DTPA Renogram	Baseline and after captopril Pre-requisites hydration, adequate salt diet and avoid RAAS blockers for 1 week. shows delayed uptake on the side of stenosis. (Fig 4). MAG3 may be more reliable in patients with renal insufficiency.	-Sensitive in unilateral renal artery stenosis -Used to decide regarding nephrectomy if kidney contributes <15% GFR and is the source of hypertension, (ii) may help assess the hemodynamic significance of a stenotic lesion (iii) helps in assessment of differential renal function	-sensitivity and specificity are not very high
Conventional angiogram	Stenosis >75% or >50% with post stenotic dilatation or a blood pressure gradient of at least 10-20%i.e. drop of 10-20 mm Hg in translesional pressure	Gold standard	-Radiation dose -Contrast nephropathy -Cholesterol embolism
CT angiogram	Same as conventional angiogram	Specificity and sensitivity >90% for ARAS	-distal, non-ostial segments poorly imaged -Specificity and sensitivity - 25% in FMD
MRA	Same as conventional angiogram	-Specificity/sensitivity 90%- ARAS -Breath-hold MRA for visualization of accessory arteries. -Sensitivity & specificity 98-100 % -Blood oxygen level-dependent MR- no radiation	-Specificity/sensitivity 25% in FMD -Gd MRA contraindicated if GFR < 30ml/min. risk of nephrogenic systemic fibrosis.

Table 3 b- Older tests for RAS			
Plasma renin	N= <1ng/ml/hour, PRA> 12mg/ml/hr highly suggestive of RVH Captopril stimulated renin test is done 1 hour after 25mg captopril..		-Levels may be normal in volume overload , high salt diet or bilateral disease or intrinsic renal disease -Obsolete
Renal vein renin	Unilateral high levels (renin that is ≥1.5 times the value from the contralateral kidney), and suppressed in the contralateral kidney (sample obtained from the infrarenal inferior vena cava)	May be used for identifying stenotic kidney before nephrectomy	-Invasive -Not specific or sensitive
Intravenous Venous Urogram	Disparity in renal size Delayed nephrogram in 1 minute film, delayed excretion on stenotic side Ureteric notching by collaterals	Radiation	Not used

Table 4	
Indications of revascularization	**Contra-indications of revascularization**
(I) Hypertension does not respond to medical management (ii) Progressive deterioration of renal functions (iii) Suspected FMD in a young person to limit the need for life-long antihypertensive therapy and (iv) Recurrent flash pulmonary edema and/or refractory heart failure	(I) Hypertension is well controlled with medicines (ii) If renal function is stable (iii) If kidneys are already atrophied (very small)

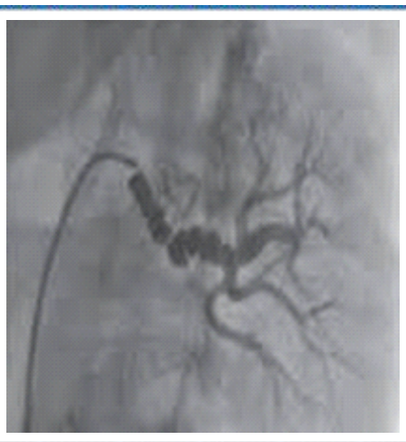

Figure 1- Fibromuscular dysplasia (sting of beads sign)

MEDIBEATS
The Medical Bulletin

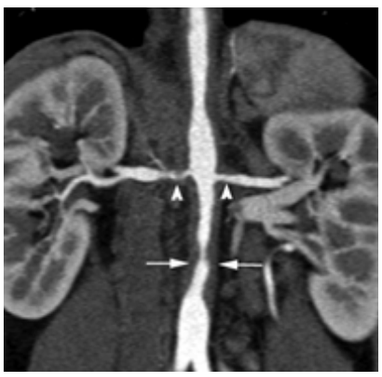

Figure 2- Takayasu's arteritis – irregular aorta and bilateral renal artery stenosis

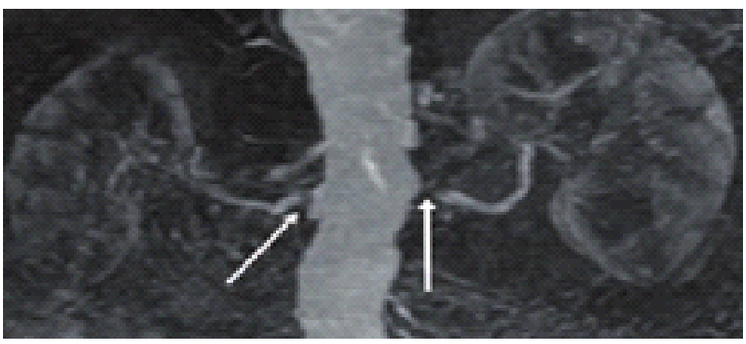

Figure 3- Atherosclerotic bilateral renal artery stenosis

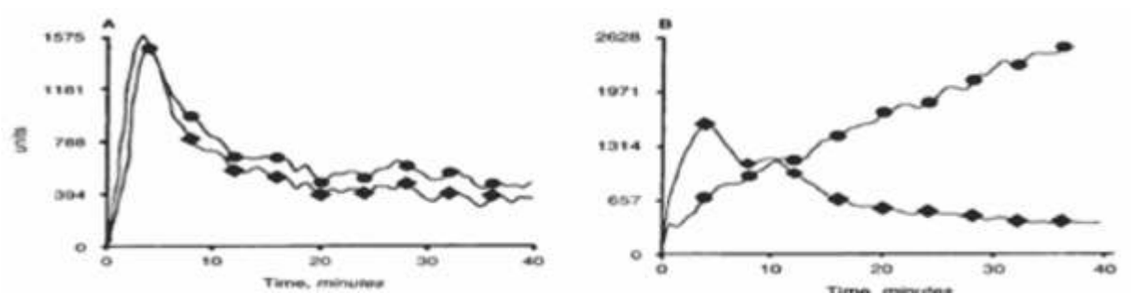

Figure 4- Captopril renogram- (A) before captopril (B) after captopril

Dr. Manisha Sahay
Professor and Head Department of Nephrology
Osmania Medical College and General hospital,
Hyderabad, Telangana, India