Review Article

Renovascular Hypertension

M. Kanitkar

Renovascular hypertension results from a lesion that impairs blood flow to a part or all, of one or both kidneys. 3-10% of children referred for the evaluation of severe hypertension are subsequently found to have clinically significant renovascular lesions Renovascular hypertension is the second most common cause of correctable hypertension in children second only to coarctation of the aorta. Specific therapeutic options now available, justify the often-invasive investigations required to confirm the diagnosis of renovascular hypertension. A systematic evaluation of the child with hypertension will help the pediatrician select correctly, the child most likely to have renovascular hypertension, thus reducing the number of children exposed to the risks involved with diagnostic but invasive investigations like renal arteriography which remains the gold standard Other non-invasive newer modalities like doppler ultrasonography, computed duplex sonography, ACE inhibited radionuclide imaging, and MR/CT/spiral CT angiography may be used depending on the availability of the facilities. Definite therapeutic options for renal artery stenosis include angioplasty, stenting and surgical re-vascularization using a bypass graft.

Hypertension in children is defined as blood pressure >95th percentile for age, gender and height on repeated measurements(1). A recording below the 90th percentile is considered normal. Children with blood pressure between the 90th and 95th percentiles should remain under observation and evaluated for other risk factors for hypertension.

Renovascular hypertension is defined as hypertension resulting from a lesion that impairs blood flow to a part or all, of one or both kidneys. Three to ten percent of children referred for evaluation of severe hypertension are found to have clinically significant renovascular lesions(2); 5.7% of such children, evaluated at a tertiary referral centre in India, had renovascular hypertension(3). Renovascular hypertension is the second most common cause of correctable hypertension in children second only to coarctation of the aorta. In view of currently available therapeutic options, a detailed evaluation for hypertension leading to a diagnosis of renovascular hypertension can be rewarding.

Renin-Angiotensin-Aldosterone System (RAAS)

An understanding of the RAAS is vital to the understanding and evaluation of renovascular hypertension. The RAAS is a hormonal system with additional paracrine and autocrine functions. Renin causes the cleavage of angiotensinogen to form angiotensin I, which is further broken down to angiotensin II by the angiotensin converting enzyme. Renin appears to be the rate-limiting enzyme in the RAAS cascade. Angiotensin II is a potent vasoconstrictor that stimulates the synthesis and secretion of aldosterone and regulates renin secretion *via* a negative feedback mechanism. It promotes sodium reabsorption at the proximal tubule, stimulates

From the Pediatric Nephrology Unit, Department of Pediatrics, Command Hospital, Pune 411 040, India.

Correspondence to: Lt. Col. Madhuri Kanitkar, Associate Professor of Pediatrics, Department of Pediatrics, Command Hospital, Pune 411 040. E-mail: madhurikanitkar@rediffmail.com

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prostaglandin release and modulates angiotensin receptor density in the vascular bed. It promotes neovascularization and cellular growth. Centrally, it stimulates thirst and release of the antidiuretic hormone.

The measurable components of the RAAS are plasma renin activity (PRA) and aldosterone. The PRA is dependent on age, posture, sodium intake and prior treatment with diuretics or antihypertensive medications. It also shows a diurnal variation. It is important to have the child in a supine position for at least two hours prior to collecting a blood sample for PRA assay and is ideally collected early morning. Severe hypertension in childhood is most commonly due to some form of renal disease and the RAAS plays an important role in perpetuating it. PRA is raised in a majority of cases with significant hypertension secondary to renovascular disease or pyelonephritic scarring. However, 15% of children with unilateral and 40% with bilateral renal artery stenosis may have normal PRA(4). Angiotensin converting enzyme inhibitors (ACEI's) stimulate PRA selectively in patients with renovascular hypertension and an ACEI stimulated PRA, the 'post captopril test', has been suggested to have a sensitivity similar to captopril renography(5). Renal vein renin measurement is an important diagnostic procedure and helps in identifying surgically curable forms of renal hypertension. It is important to keep in mind the association of renovascular disease and pheochromocytoma. The tumor can cause renal artery compression and also directly stimulates renin release, resulting in raised PRA. On the other hand, renovascular hypertension with raised PRA can cause a rise in levels of urinary and plasma catecholamines.

A low PRA in a hypertensive child on the other hand suggests mineralocorticoid excess or a salt and water overload for other reasons.

Etiology

The commonest cause for renovascular hypertension in children reported in western literature is fibromuscular dysplasia (FMD) and the midaortic syndrome(4). However, in India Takayasu disease (idiopathic aortoarteritis) is the most important cause(3) accounting for upto 87% of children with renovascular hypertension(6). Renal artery stenosis may also occur in association with neurofibromatosis, Williams syndrome, Marfan syndrome, rubella syndrome, Klippel Trenaunay Weber syndrome, linear sebaceous nevus syndrome, Kawasaki disease and Crohn disease. Bilateral renal artery disease is more common than unilateral, with or without intrarenal arterial involvement. In a review of 54 children with renovascular hypertension, 38 had bilateral and 16 unilateral disease; 20% had coarctation of abdominal aorta with resultant middle aortic syndrome(7).

Clinical Features

The presentation of renovascular hypertension is generally non-specific. Children with a blood pressure >140/100 mm Hg at any age are more likely to have secondary hypertension. However the level of blood pressure may not delineate children with renal artery disease. Younger children may present with irritability, behavioral changes or failure to thrive. Older children may complain of headache and lethargy. Complications arising from severe hypertension *e.g.*, left ventricular failure, neurological complications like Bell's palsy, seizures or intracranial bleeds may be seen at presentation. Metabolic problems may include hypokalemic alkalosis, or renal insufficiency; ESRD at presentation is rare(4).

A meticulous history and clinical examination may raise a high index of suspicion for renovascular hypertension.

Just as a history of urinary tract infections suggests renal parenchymal disease, a history of umbilical catheterization in the neonatal period, abdominal irradiation and a renal transplant may point to a possible renovascular problem. Systemic symptoms like fever, weight loss, diffuse myalgias, features of vascular insufficiency, preceeded by pain over involved arteries and absent pulses suggest aortoarteritis. Café-au-lait spots and other features of neuro-ectodermal syndromes need to be looked for along with a bruit over the abdomen or other larger vessels. Though the presence of a renal bruit is highly suggestive of renal artery stenosis, 13% of children with a renal bruit may be normal on an arteriography and conversely only 30% of children with renal artery stenosis may have a bruit(4).

Evaluation

Investigating a child with hypertension aims at determining a possible renovascular cause and then confirming it with more specific tests. It also necessitates the evaluation of end organ damage resulting from the severe hypertension with echocardiography and opthalmological examination, as well as the possible underlying etiology for renal artery stenosis. Clinical criteria to diagnose aortoarteritis have been described(8) and include one obligatory criterion (age less than or equal to 40 years), two major criteria (left and right mid-subclavian artery lesions) and nine minor criteria (high erythrocyte sedimentation rate, common carotid artery tenderness, hypertension, aortic regurgitation or annuloaortic ectasia and lesions of the pulmonary artery, left mid common carotid artery, distal brachiocephalic trunk, thoracic aorta and abdominal aorta). In addition to the obligatory criterion, the presence of two major criteria, or one major plus two or more minor criteria, or of four or more minor criteria suggests a high probability of the presence of Takayasu disease. In Asians the disease may present at a later age and involvement of the abdominal aorta causing renovascular hypertension is seen more frequently(9). Reports have linked aortoarteritis with a variety of infectious agents including spirochetes, bacteria, mycobacteria and viruses. However, there is no convincing evidence that any of these play a pathogenic role(10). Efforts to rule out tuberculosis through circumstantial evidence, in the form of chest radiography, Mantoux test and lymph node biopsy, are required. Disease activity index is determined using ESR, and C-reactive proteins along with clinical and angiographic criteria(11)

Renal arteriography is the gold standard for confirming the diagnosis of renal artery stenosis, but is an invasive procedure. The diagnostic risk-benefit issues relating to the diagnosis of renovascular hypertension raise the question of whether a pediatrician can select correctly the child likely to have renovascular disease prior to planning arteriography. Rapid sequence intravenous urography (IVU) is not a reliable investigation. The most reliable abnormality on IVU predicting stenosis is a size difference between the kidneys, for which ultrasonography is a better tool.

Clinical features and baseline investigations warranting further evaluation for renovascular hypertension are shown in *Table I.* Children with sustained hypertension and no evidence of renal scarring, glomerular disease, catecholamine excess or any other identifiable cause should also be evaluated further for a possible renovascular cause

Specific Tests

These include doppler ultrasonography, computed duplex sonography, captopril

TABLE I –*Indications for Evaluation for Renovascular Disease.*

Clinical features	Investigations
• Renal/peripheral bruits	• Hypokalemia
• *Café au lait* spots	• Increased urea/creatinine
• Absent pulses	• One kidney smaller on scanning
• Blood pressure >99th centile with no obvious cause or difficult to control blood pressure	• Raised plasma renin activity

renography, radionuclide imaging, and magnetic resonance (MRA) or computerized tomographic (CT) angiography depending on the availability of the facilities. These tests are relatively non-invasive and can help decide which patients need conventional arteriography for confirmation of the diagnosis of renovascular disease. Their sensitivity and specificity are shown in *Table II*. Renal vein renin assays have an important role in helping make therapeutic plans for a child with renovascular hypertension. A systematic evaluation of the child with hypertension (*Fig. 1*) will help the pediatrician select correctly, the child most likely to have renovascular hypertension, thus reducing the number of children requiring invasive investigations like renal arteriography.

Doppler Ultrasonography

This test in expert hands can demonstrate the changes in the flow within the renal arteries and computed duplex sonography can measure blood flow volumes. Doppler studies can detect stenotic lesions only when they are severe. A peak systolic velocity greater than 180 or 200 cm/s and renal aortic ratio greater than 3.0 is suggestive of renovascular hypertension(12).

Radionuclide Scans

The standard 99^{m}technetium diethylene triamine penta acetic acid (DTPA) scan and ^{131}I-orthoiodohippurate scan are useful investigations to detect renal artery stenosis. A repeat DTPA scan after captopril (captopril renogram) allows identification of over 90% children with unilateral renal artery stenosis(13). In children with renovascular hypertension captopril induces changes in the scintigraphic images of the kidney distal to the stenosis by revealing a reduced uptake or delayed excretion with cortical retention. Cortical retention is however difficult to interpret in the presence of suspected pelvic retention and there may be marked inter-observer variability. In a recent multicentric trial, looking for inter-observer variability in

TABLE II–*Utility of Investigations for Diagnosing Renovascular Hypertension.*

Modality	Sensitivity	Specificity
Doppler ultrasonography(12)	92%	88%
CT angiography(16)	94%	98%
MR angiography(15)	100%	94%

Conventional renal arteriography is the gold standard.

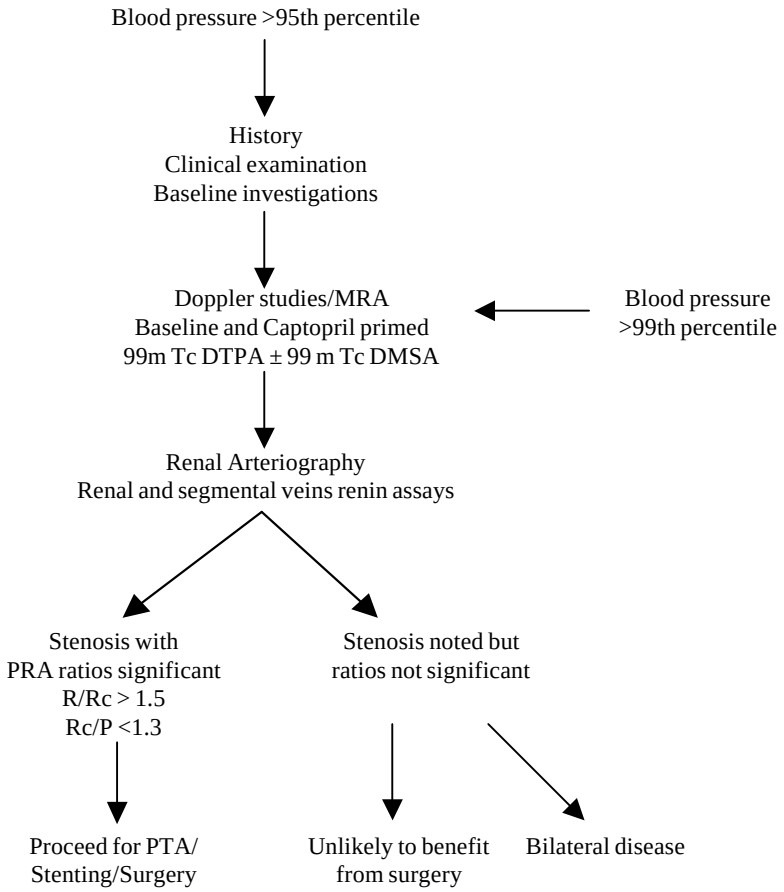

Fig. 1. Management of renovascular hypertension in children. R: Renal vein renin, affected kidney; R_C: Renal vein renin, contralateral kidney; P: low inferior vena cava renin.

the interpretation of 1205 DTPA scans, the sensitivity of the captopril renogram ranged from 70-100% and specificity 60-100%(14). The utility of the captopril primed 99mTc dimercaptosuccinic acid scan (99^{m}Tc-DMSA) in identifying renal abnormalities especially scarring is valuable, as it may identify etiologies of renovascular hypertension other than renal artery stenosis.

MRA/CT/Spiral CT Angiography

MRA is a time efficient and safe test when compared with conventional arteriography. Gadolinium enhanced MRA has proven to have a high sensitivity for detecting stenosis in the main and accessory renal arteries. A 3-D phase contrast MRA can improve the specificity of the test(15). CT/spiral CT angiographies have the advantage of being less invasive and fairly useful in the diagnosis of renovascular hypertension(16), though with a higher radiation and contrast burden. Their role in the evaluation of children with renovascular hypertension is controversial, as they may not demonstrate stenosis of intrarenal vessels in all cases.

Digital Subtraction Angiography (DSA)

Intravenous digital subtraction angiography has the potential for direct detection of renal artery stenosis with intravenous injection of contrast. It may not be good enough for intrarenal abnormalities. Intra-arterial DSA though as invasive as the renal arteriography, requires half the volume of diluted contrast medium for good visualisation of renal vessels and therefore causes less radiation exposure than with the standard angiography. A 3-D DSA has an advantage over conventional 2-D DSA especially in the diagnosis of aneurysms.

Renal Angiography

Renal arteriography remains the gold standard, but is an invasive procedure and should be undertaken when the index of suspicion for renal artery stenosis is high. Direct intra-arterial contrast injection with computer aided digital subtraction appears to be the definitive procedure for the evaluation of children with renovascular hypertension.

Renal Vein Renin Assays

In children, measurement of selective renal vein renin is useful to confirm the hemodynamic significance of confirmed renal artery stenosis. Renal vein renin ratios of >1.5:1 between the affected and the contralateral kidney are considered significant and predict a satisfactory response to surgery. This prediction is reinforced by a PRA ratio <1.3 of contralateral renal vein renin to inferior vena cava renin assay(17). Segmental renal vein sampling allows demonstration of lateralization when arterial disease is segmental. When these differences are not obvious, bilateral disease is suspected. Facilities for these tests are not readily available.

Treatment

Relieving the stenosis and restoring renal blood flow would seem the obvious solution to curing renovascular hypertension. But in a large number of children this may not be easily achieved due to the disease being extensive and bilateral. These children and also those awaiting surgical intervention need medications to control the blood pressure. It is advisable to avoid diuretics like frusemide, as they worsen salt and water depletion, which can aggravate the release of renin. ACEI are effective; however need close monitoring of renal functions in view of the ability to cause a drop in the glomerular filtration rate. They are probably best avoided until angiographic data and results of captopril primed scans are available. When used in unilateral renal artery stenosis it has a significantly favorable outcome with a reduction in proteinuria as well, but can cause a decrease in function of the kidney.

In Takayasu disease (idiopathic aorto-arteritis), treatment is based on the use of glucocorticoids alone or in association with a variety of cytotoxic medications, the one most commonly used being methotrexate. The dose is titrated in relation to the ESR, to remain below 20 mm per hour. Therapy with corticosteroids needs to be continued for 2-3 years followed by gradual tapering and eventually withdrawn if and when no clinical signs of flare up are evident and the ESR is persistently <10 mm per hour(11). The disease is likely to flare up on withdrawing corticosteroids and may then require more aggressive immunosuppression. A positive tuberculin sensitivity test or a diagnosis of accompanying active tuberculosis necessitates antituberculous therapy. In a series of thirty children from South Africa with Takayasu arteritis, 90% had a strongly positive Mantoux test and were treated with

Key Messages

- Renovascular hypertension is the second most common cause of correctable secondary hypertension in children.
- Aortoarteritis is the commonest cause for the renal artery stenosis in India.
- A systematic approach will select the child most likely to have renovascular hypertension, thus reducing the number of patients requiring renal angiography.
- Therapeutic options for renal artery stenosis include percutaneous transluminal angioplasty, stenting and surgical revascularization.

antituberculous therapy(18).

Surgery

The choice of either surgery or percutaneous angioplasty depends on the age and size of the child, technical feasibility, extent of the disease process and the underlying etiology. The options most commonly used are percutaneous transluminal angioplasty (PTA), PTA with stenting and surgical revascularization. The widespread nature of the disease in children means that the majority will not benefit from surgical intervention. In a series of 54 children treated for renovascular hypertension only 20 (37%) were considered likely to benefit with a surgical intervention, 10 (18%) children underwent surgical reconstruction due to the extensive nature of their disease and 6 (10%) underwent PTA(13). PTA and PTA with stenting are relatively simple procedures. Ballooning followed by stenting often improves blood flow. Surgical revascularization is undertaken using grafts to bypass the site of obstruction. Long term studies for children with PTA/stenting have not been reported, however with a bypass graft in a series of 53 children followed up for up to 16 years the hypertension was cured in 70% and improved in another 26%(19). When the outcome and cost were compared in 130 patients treated with PTA, renal artery stenting or renal artery bypass grafting, the success rates were comparable at 91%, 98% and 92% with a complication rate of 13%, 16% and 38% respectively. All three were equally effective in controlling hypertension but the cost of surgery was ten times that of PTA and six times that of stenting(20). Some children undergo a combination of treatments, with success often difficult to link to one or other of the procedures. There is also a benefit in improving blood supply to the kidney thus reducing the antihypertensive medications, yet not curing the hypertension.

Other options available are autotransplantation of the functioning but severely stenosed kidney or a partial/total nephrectomy for a non-functioning kidney that is causing severe hypertension.

Following PTA/surgery, the blood pressure often takes some time to reduce. This may be because of postoperative edema or vasospasm of the renal artery. At times there may be an embolic episode during the PTA. Follow up with DMSA scan and doppler study carried out after the procedure can help detect these complications.

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