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Review Article

Renal Hypertension in Children

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Abstract Renal hypertension is due to or associated with congenital, inherited or acquired forms of renal disease. The commonest cause is some form of parenchymal disease with reflux nephropathy and the chronic glomerulopathies being the most important categories. Renovascular disease, although only constituting 10% of secondary hypertension in childhood, is important in view of its potential for cure by modern interventional radiological and surgical techniques. Other renal causes of hypertension include polycystic kidney disease, renal tumours and renal monogenic hypertensive disorders such as Liddle's syndrome. The majority of children with chronic renal failure (chronic kidney disease) are hypertensive and effective blood pressure control has beneficial effects on the rate of renal functional deterioration.

Key words Child; Chronic kidney disease; Hypertension; Reflux nephropathy; Renovascular

Introduction

Renal hypertension is hypertension due to or associated with congenital, inherited or acquired forms of renal disease. The causes are listed in Table 1. It constitutes a significant proportion of childhood secondary hypertension and the majority of affected children have hypertension of a severity requiring treatment. Renal hypertension can be acute and usually transient or chronic and sustained. In this review the focus will be on the latter although at initial presentation it may not be clear in individual patients which category they come into. Renovascular hypertension will be especially focussed on in view of its potential for cure.

Renovascular Hypertension

Renovascular hypertension results from a lesion or lesions that impair blood flow to a part or all of one or both kidneys. It constitutes approximately 10% of cases of secondary hypertension in childhood.[1,2]

Causes

The most common abnormality in Europe or North America is some form of renal artery stenosis which, in 70% of children with renovascular hypertension, is due to fibromuscular dysplasia.[3-9] However, this is not applicable in certain parts of the world, for example in the Indian subcontinent or South Africa, where Takayasu arteritis is relatively common.[10-14]

It seems likely that uncontrolled release of growth factors during angiogenesis play an important part in the development of fibromuscular dysplasia. The lesions often cause areas of arterial narrowing alternating with aneurysmal sections giving rise to the characteristic "string of beads" appearance on angiography. However, the angiographic appearances of the affected renal vasculature in fibromuscular dysplasia is quite variable including solitary main renal artery stenosis, bilateral disease, branch vessel involvement and widespread small vessel abnormalities. In addition, there can be extrarenal disease involving the aorta causing the mid-aortic syndrome, mesenteric artery pathology and cerebral vascular disease. Mid-aortic syndrome is seen in 20-25% of cases of renovascular disease,[15-18] mesenteric disease in 20-30%[2,18]

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and cerebrovascular disease in 20-40%[2,18,19] depending on which series is being analysed.

There are many other causes of and associations with renovascular disease in children resulting in hypertension (Table 2). The commonest of these is neurofibromatosis in which intimal hyperplasia is usually seen histologically.[20-26] However, other neuroectodermal syndromes, such as the Feuerstein-Mims syndrome, can also be associated with lesions in the renal and extra-renal vasculature.[2] Additionally, renovascular hypertension is recognised in other syndromes including the velo-cardio-facial syndrome,[27] pseudoxanthoma elasticum,[28] Klippel-Trenaunay-Weber syndrome,[2] idiopathic hypercalcaemia,[29,30] Marfan's syndrome[31] and rubella syndrome.[32] Thromboembolic lesions can also cause renal artery stenosis following umbilical artery catheterisation[33] and thrombosis of the ductus arteriosus.[33] Systemic vasculitides affecting medium or large arteries can be a cause, especially in polyarteritis nodosa,[34] Kawasaki disease[35] and Takayasu arteritis.[10,14] In Takayasu disease the aorta and its major branches are affected, including the renal vasculature, causing hypertension and, in time, renal impairment. Other causes include renal arterio-venous fistulae,[36] renal artery aneurysm,[37] abdominal radiation,[38,39] trauma[3,40] and external lesions compressing the renal vasculature.[2,41,42] Renal transplantation is another well known cause resulting from renal arterial stenotic lesions developing in the graft artery in 2-10% of cases.[43,44] This might be at the site of anastomosis or in the donor artery proximally as a result of an immunologically determined inflammatory process.[45]

Table 1 Causes of renal hypertension

Renovascular disease
Renal parenchymal disease
Reflux nephropathy
Chronic glomerulopathies
Renal dysplasia/inherited polycystic diseases
Other renal damage e.g. post haemolytic uraemic syndrome
Renal tumours
Chronic kidney disease/transplantation
Renal monogenic hypertension e.g. Liddle's syndrome

Clinical Manifestations

The clinical presentation of children with renovascular hypertension is variable. Some are entirely asymptomatic,[46] while others present with more characteristic features, including headache (in older children) or nausea, vomiting or failure to thrive (in younger patients).[2] Unfortunately the first sign of hypertension might be the development of an accelerated hypertensive state with fits, hemiplegia, visual symptoms or facial palsy. There may be evidence of a syndrome associated with renovascular disease and there may be bruits over the abdomen, flanks, neck or head. However, physical examination may be entirely negative in the presence of significant renovascular pathology.

Evaluation

Patients with renovascular hypertension often present with a degree of hypokalaemic alkalosis due to secondary

Table 2 Causes of and associations with renovascular disease

Fibromuscular dysplasia	–
Neuroectodermal syndromes	Neurofibromatosis Feuerstein-Mims
Other syndromes	Velo-cardio-facial, pseudoxanthoma elasticum, Klippel-Trenaunay-Weber, Idiopathic hypercalcaemia, Marfan's, rubella
Thromboembolic lesions	Umbilical artery catheterisation, Thrombosis of ductus arteriosus
Systemic vasculitides	Polyarteritis nodosa, Kawasaki disease Takayasu arteritis
Miscellaneous causes	Renal arterio-venous fistula, renal artery aneurysm, Abdominal radiation, trauma, external pressure
Renal transplantation	–

hyperaldosteronism. Renal impairment may be present due to severe arterial narrowing or secondary to accelerated hypertensive renal damage. Urine analysis is usual unhelpful although proteinuria and haematuria can occur in the presence of severe hypertension. If measured, plasma renin activity is usually increased when compared to age related normative data.[47] The gold standard investigation is digital subtraction renal angiography.[47-49] Although magnetic resonance angiography[50,51] and computed tomographic angiography[50-52] are also available in major centres they are generally inappropriate for use in children, except in special circumstances, due to a lack of sensitivity and specificity and an inability to adequately demonstrate detailed intra-renal arterial anatomy. Additionally, computerised tomographic angiography carries with it a severe radiation burden that is unacceptable in childhood. Other procedures can have roles in evaluation of patients suspected of suffering from renovascular disease. These include ultrasonography (pulse-wave and colour Doppler), isotope renography (static and dynamic plus captopril primed) and renal vein renin determinations.

Standard ultrasonography might reveal data on relative kidney size and also on the presence of other renal pathology that might point to an alternative cause for the hypertension. Pulse-wave and colour Doppler techniques are more revealing and can identify stenotic lesions in both main and major branches of the renal arteries.[53-55] However, specificity and sensitivity is inadequate for this approach to reliably identify renovascular pathology.[51,56-58] Likewise isotope renography might suggest a renovascular cause for hypertension, especially captopril primed studies,[59-61] but again are not sensitive or specific enough for diagnostic purposes.[51,62-65] Renal vein renin sampling has, in good hands, been shown to identify kidneys or parts of kidneys that are releasing excess renin and to provide predictive information as to whether interventional treatment will prove successful in curing or reducing hypertension.[66,67]

Treatment

The options available in treating renovascular hypertension are antihypertensive medication, interventional radiology (angioplasty, stenting, embolisation) and surgery (nephrectomy, partial nephrectomy, revascularisation by direct arterial anastomosis, by-pass grafting or autotransplantation).

Medical Management

Anti-hypertensive drug therapy is necessary whether other intervention is going to be subsequently needed or not. Drugs used include ACE inhibitors, calcium channel blockers, beta blockers and diuretics.[68-70] Occasionally angio-receptor antagonists, vasodilators, central alpha agonists and peripheral alpha antagonists are indicated, especially if blood pressure is resistant to treatment. Caution is necessary with ACE inhibitors in patients with solitary kidneys, bilateral renal artery stenosis or in patients with very severe stenotic lesions affecting just one kidney since there is the risk of precipitating loss of renal function.[68] Diuretics should also be used with caution since most patients with renovascular hypertension are salt and water depleted on presentation due to the natriuresis that the hypertension causes from the unaffected kidney or from parts of the kidneys with normal vascular supply. In children with significant cerebrovascular pathology caution must be exercised to ensure that blood pressure does not drop precipitously causing serious cerebral or optic nerve ischaemia.[19] Once blood pressure is adequately controlled then decisions are necessary about whether intervention is necessary by interventional radiological procedures or surgery.

Angioplasty / Stenting / Embolisation

With the increasing sophistication of interventional radiology angioplasty is becoming the preferred first option when decisions are being taken as to the type of intervention indicated after medical control of blood pressure.[71-74] Recent data from Great Ormond Street Hospital for Children[27] showed that of 33 children treated by angioplasty 48% had bilateral disease, 45% had intrarenal disease, 24% mid aortic syndrome, 21% had cerebrovascular disease. Hypertension was cured in 27%, improved in 21%, maintained high purposely because of cerebrovascular pathology in 6%, there was no change in blood pressure despite technical success in 30% and there was technical failure in 15%. Overall 85% of children with main artery disease were improved in terms of blood pressure control but only 30% children benefitted in those with intrarenal disease or extrarenal arterial stenoses. A high rate of restenosis was recorded after stenting. There was 1 death and 5 minor complications. These results are similar to those from the more recent literature. Earlier reports are difficult to compare since techniques were less refined and less complex cases were usually subjected to the procedures. Embolisation of small renal vessels has also been occasionally utilised in circumstances where angioplasty or surgery are not feasible.[75]

Surgery

Not all children with renovascular hypertension will be

amenable to percutaneous transluminal angioplasty and there will be others in whom there has been a lack of response or re-stenosis after an initially successful procedure. In these circumstances, if feasible, a surgical approach would be indicated. Nephrectomy may be justified in circumstances of unilateral disease when angioplasty or re-vascularisation surgery is not possible or has failed and renal function of the affected kidney is poor or absent. Partial-nephrectomy might be indicated if localised, intrarenal, disease affecting the vasculature in a polar region is not amenable to angioplasty or re-vascularisation surgery and overall renal function would not be compromised by the procedure.[2,67] There are exceptions to these general rules and, at times, children with an affected kidney contributing, for example, more than 10% function may require nephrectomy if no other option is available. Revascularisation procedures are, however, the more common way to proceed and tend to utilise autologous revascularisation techniques, graft revascularisation and aortic reconstruction with or without grafting.[2,3,37,76-80] Data from Michigan in the United States showed that in 97 children treated surgically between 1963 and 2006, 132 primary operations and 30 secondary operations were undertaken.[81] There was operative benefit in 98%, hypertension was cured in 45 (79%), hypertension was improved in 11 (19%), hypertension was unchanged in 1 (2%) and there were no operative deaths. In comparison results of surgical treatment for renovascular hypertension over a 30 year period at Great Ormond Street Hospital have recently been published.[82] Of the 37 children treated surgically 49% had bilateral disease, 40% had intrarenal disease, 40% had mid aortic syndrome, 24% had visceral artery involvement and 26% had co-existing cerebrovascular disease. There were 52 surgical procedures: 15 primary nephrectomy, 17 autologous revascularisation, 9 graft revascularisation, 6 aortic reconstruction with graft and 1 without graft. Technical failure led to unplanned or secondary nephrectomy in 4 patients. There were no operative deaths. The outcome showed that 18 patients (49%) had normal blood pressure without treatment, 14 patients (38%) had an improved blood pressure and in 4 patients (10%) blood pressure was unchanged. Reduction of blood pressure led to loss of the contralateral kidney in 2 patients. Eight children required 12 further angioplasties: in 4 for new lesions and in 8 for graft stenoses. These findings suggest a less good outcome than those from the Michigan group but it has to be born in mind that the complexity of the vascular anatomy and the young age of many of the children suggest a very different and higher risk patient population with hence potentially less chance of complete "cure" by surgical intervention. Finally in this context it must be remembered that a not inconsequential number of children with renovascular hypertension have to be treated medically since they are, for various reasons, unsuitable for interventional radiological or surgical intervention.

Renal Parenchymal Disease

Renal parenchymal diseases causing hypertension in childhood include reflux nephropathy, the chronic glomerulopathies, congenital renal anomalies e.g. renal dysplasia, inherited renal disorders e.g. autosomal dominant and recessive polycystic kidney diseases and other acquired renal diseases such as HUS precipitated kidney damage (Table 3).

Table 3 Renal parenchymal disease

Reflux nephropathy/obstructive uropathy	–
Chronic glomerulopathies	Focal glomerulosclerosis Membranoproliferative (mesangiocapillary) glomerulonephritis Henoch-Schonlein nephritis IgA nephropathy Alport's syndrome Lupus nephritis Wegener's granulomatosis etc.
Congenital renal anomalies	Renal dysplasia
Inherited cystic disorders	Autosomal recessive polycystic kidney disease Autosomal dominant polycystic kidney disease etc.
Other acquired diseases	Post infectious glomerulonephritis Nephropathy post haemolytic uraemic syndrome etc.

Reflux Nephropathy

This can be defined as the coarse renal scarring associated with vesico-ureteric reflux and previous urinary tract infection. Similar parenchymal damage can also occur in relation to obstructive uropathies plus infection. It is one of the commonest secondary causes of hypertension in childhood.[83] Approximately 10% of children with reflux nephropathy will develop hypertension.[84] By late adolescence this will be of the order of 18-20%[85] and from long term follow up studies it would seem that 30-40% of subjects will eventually become hypertensive.[86,87]

Evaluation of such patients focuses on the demonstration of renal scarring of the characteristic appearances and exclusion of other causes for the hypertension. In days gone by the intravenous urogram was the means of demonstrating this and, although superceded by newer techniques, it occasionally still has a role in clarifying the nature of scarring by demonstrating the characteristic loss of cortical thickness and clubbed calyces at sites of scarring.[88] Currently ultrasonography has a low sensitivity compared with isotope renography using Tc99-DMSA scanning in detecting renal scarring but both are currently utilised.[89,90] The presence or history of vesico-ureteric reflux supports the diagnosis but it needs to be remembered that the absence of reflux does not exclude it. A raised plasma renin activity for age is often a feature but this is not consistent and does not predict hypertension in the future.[85,91]

Treatment is essentially medical utilising standard anti-hypertensive drugs.[92] The role of surgery is not clear although occasionally nephrectomy might be considered especially in unilateral disease on the affected side. Control of blood pressure is important since episodes of uncontrolled hypertension have been clearly shown to have serious adverse effects on long term renal function.[93] Individuals with extensive scarring are at greater risk of developing hypertension and of progressing to chronic renal failure, with its own contribution to maintaining hypertension.[94,95]

Chronic Glomerulopathies

The chronic glomerulopathies are also a common cause of secondary hypertension in childhood.[96] Included in this category are: focal segmental glomerulosclerosis, mesangiocapillary (membranoproliferative) glomerulonephritis, Henoch-Schonlein purpura, IgA nephropathy, Alport's syndrome, lupus nephritis, Wegener's granulomatosis etc. The diagnosis is usually established by the characteristic clinical history, in some cases the finding of typical complement and serological profiles and by undertaking a renal biopsy revealing diagnostic light microscopical changes, immunofluorescent findings and electron microscopical appearances. Management is essentially that of the underlying condition but, in time, often becomes the management of chronic renal failure if renal function progressively deteriorates, as is likely, in many of the listed conditions. However, control of hypertension is critically important on the basis that, if uncontrolled, the adverse effects on renal function are serious.[97,98] Standard anti-hypertensive drug therapy would be indicated in addition to other appropriate measures in terms of handling children with deteriorating renal function.[99]

Other Parenchymal Disorders

Hypertension is particularly common in autosomal recessive and dominant polycystic kidney diseases.[100,101] In other disorders, for example, following diarrhoea associated haemolytic-uraemic syndrome hypertension is variable although can and does occur.[102] In atypical (non-diarrhoea-associated) haemolytic-uraemic syndrome, in contrast, hypertension is a major problem.[103]

Renal Tumours

Three sorts of tumour affecting the kidneys can cause hypertension. These are: Wilm's tumour, haemangiopericytoma and hamartoma. More than 50% of Wilm's tumour patients are hypertensive.[104] The mechanism for this is thought to be excess renin production either by the tumour itself or by intrarenal artery compression by the tumour. Haemangiopericytomata are rare tumours of the juxta-medullary cells that also cause hypertension by excess renin release.[105-107] They are usually less than 1 cm in diameter and difficult to identify. Arteriography generally fails to locate the lesion but CT scanning has a much better diagnostic record.[108] Renal vein renin sampling may also prove helpful in localising the site of such a tumour. Treatment is surgical, ideally by heminephrectomy. If suspected, but not identified, then ACE inhibitor or angiotensin receptor antagonist treatment may be preferable to speculative total nephrectomy, at least in the first instance, since there is no evidence that these tumours are malignant. Renal hamartomas have also been known to be associated with hypertension with similar mechanisms playing a part in causality.[109]

Hypertension Associated with Chronic Renal Failure (Chronic Kidney Disease)

Hypertension is present in approximately 50% of

children with chronic renal failure, now called chronic kidney disease (CKD).[110] However, by end-stage, 95% will be hypertensive. It is also clear that hypertension is a major factor in the progressive deterioration of renal function in such patients. Data from adults with chronic kidney disease and proteinuria demonstrate slower progression of CKD with adequate blood pressure control.[111] Hypertension also contributes to cardiovascular risk in adults and children with CKD.[112] A recent study (the ESCAPE trial) has shown that in children with CKD intensified blood pressure control, with target 24-hour ambulatory blood pressure levels in the low range of normal, confers substantial benefit with respect to renal function in this group of children.[113] Most available clinical evidence has been obtained with drugs blocking the renin-angiotensin system. They have a powerful anti-proteinuric action and in one study comparing the effects of an angiotensin receptor blocker (irbesartan) with a calcium antagonist (amlodipine) in children with non-diabetic CKD the anti-hypertensive effects were similar but significant reduction in proteinuria only occurred with the irbesartan treatment.[70,114,115] Additionally, once end stage renal failure has ensued and patients are on haemodialysis, hypertension still remains a problem. In the United States 79% of patients included in a long term study were hypertensive and 62% of them required anti-hypertensive therapy.[116] In children on chronic peritoneal dialysis the incidence of hypertension has been reported as 54%.[117] Hypertension is a common phenomenon after renal transplantation with up to 70% of paediatric transplant patients requiring anti-hypertensive medications in the first month after transplantation.[118] Factors contributing to this include a history of pre-transplantation hypertension, persisting native kidney hypertension, the effects of immunosuppressive medication, transplant renal artery stenosis and chronic allograft dysfunction.

Renal Monogenic Hypertension

There are a number of inherited conditions of the corticosteroid pathway that cause hypertension by the action of circulating mineralocorticoids on normal kidneys. Examples of these types of condition include 11 beta hydroxylase deficiency, 17 alpha hydroxylase deficiency and glucocorticoid-remediable aldosteronism. In contrast there are three other monogenic forms of hypertension where the sites of the inherited pathological mechanisms reside within the kidney and can, hence, be considered as renal in origin.[119,120] These low renin hypertension disorders are: Liddle's syndrome (dominantly inherited over-activity of the epithelial sodium channel in the cortical collecting duct),[121,122] apparent mineralocorticoid excess (recessively inherited deficiency of the renal isoform of 11 beta hydroxysteroid dehydrogenase in the distal renal tubule and cortical collecting duct)[123,124] and Gordon's syndrome (dominantly inherited gain of function mutations encoding WNK1 and WNK4 in the distal convoluted tubule and cortical collecting duct).[125,126] Liddle's syndrome and apparent mineralocorticoid excess characteristically are associated with hypokalaemia whereas Gordon's syndrome with hyperkalaemia. Liddle's syndrome is treated with triamterine or amiloride, apparent mineralocorticoid excess with dexamethasone to suppress cortisol production but often spironolactone and even sodium channel blockers are required, Gordon's syndrome is usually treated with hydrochlorothiazide or frusemide.

Conclusion

As can be seen renal disease is an important cause of secondary hypertension in children. The development of increasingly sophisticated investigative and therapeutic tools has paved the way towards more accurate diagnosis and effective treatment. This has been particularly relevant to renovascular disease, where, refined angioplastic and surgical techniques have permitted complex, hitherto uncorrectable, vascular lesions to be managed successfully. The control of hypertension in chronic kidney disease is making an impact on the rate of deterioration of renal function in affected patients and the development of newer anti-hypertensive agents is ensuring much more effective blood pressure control in childhood hypertension generally. Molecular genetic advances, in addition to clarifying monogenic causes of hypertension may, eventually, throw more light on the kidney's role in contributing to the high blood pressure in, for example, the increasingly common problem of childhood primary hypertension.

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