Malignant hypertension in children in India

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Abstract
Background. Malignant hypertension is now an uncommon entity in the western world but still remains a significant problem in India. Therefore we studied the aetiological spectrum, management, and outcome of these patients.

Methods. Forty consecutive children (<16 years) with malignant hypertension were admitted and investigated to exclude or confirm the secondary causes of hypertension. For acute control of blood pressure sublingual nifedipine was used in dosage of 0.3–0.6 mg/kg, failing which intravenous nitroglycerin was used. In patients with aortoarteritis with active disease, steroids were used. Angioplasty was carried out for renal artery stenosis whenever possible.

Results. Renoparenchymal disease was the commonest cause of malignant hypertension, and was seen in 25 cases, renovascular hypertension in 13 cases (11 aortoarteritis and two fibromuscular dysplasia), and two had essential hypertension. For acute control of severe hypertension, sublingual nifedipine was effective in 92.5% of patients. Of the patients with renoparenchymal disease five became normotensive with treatment of the underlying disease, four received renal allograft, seven died, and nine are stable on antihypertensive drugs. Renal angioplasty was carried out in seven patients with renovascular hypertension (4 cured, 3 improved) and six are controlled on drugs.

Conclusions. We conclude that apart from renoparenchymal disease, aortoarteritis is a common cause of malignant hypertension in children. Sublingual nifedipine is effective for the rapid control of severe hypertension, and angioplasty is effective in aortoarteritis for short-term preservation of renal function and control of hypertension.

Key words: aortoarteritis; renovascular hypertension; treatment

Introduction
Malignant hypertension (MHT) has been a well-recognized entity since the beginning of this century [1]. MHT has been defined as severe elevation of blood pressure with grade III (bilateral haemorrhage and exudates) or grade IV (bilateral papilloedema) hypertensive retinopathy and the presence of end-organ damage [2–4]. Hypertension is common in the general population, but the development of a malignant phase is now a rare event. In earlier studies the incidence of malignant hypertension varied from 1 to 7% and the average survival of patients with malignant hypertension was 10.5 months [5,6]. In the past two decades early recognition and prompt treatment with effective antihypertensive drugs has led to a true reduction in the number of patients developing malignant hypertension, and a dramatic improvement in survival.

Most of the earlier studies on hypertension in children have included those with severe persistent hypertension [7–11]. We report here the aetiological spectrum, management, and outcome of 40 children admitted with malignant hypertension.

Subjects and methods
In the last 6 years 40 consecutive paediatric patients (<16 years) admitted with the malignant or accelerated form of hypertension were studied. There were 27 males and 13 females with a mean age of 12 years (range 3–16 years). In all cases the diagnosis of malignant hypertension was based on the presence of grade III (bilateral exudates or haemorrhage) or grade IV (bilateral papilloedema) hypertensive changes in the fundus and severe hypertension (definition given by Second Task Force on Control of Blood Pressure in Children) (Table 1) [12].

All the patients underwent investigations to exclude or confirm secondary hypertension. The investigations included complete haemogram, erythrocyte sedimentation rate (ESR), creatinine, blood urea nitrogen (BUN), serum electrolytes, calcium, phosphorus, alkaline phosphatase, triglycerides, and cholesterol. Urine was examined microscopically and 24-h urinary protein, creatinine, urinary electrolytes, and vanilmandelic acid (VMA) excretion was also estimated. The radiological investigations were chest X-ray, ultrasonogram of abdomen (USG), and intravenous urogram (IVU).
Renal parenchymal disease (RPD)

The diagnosis of chronic glomerulonephritis (CGN) was made on kidney biopsy in patients with normal-sized kidneys and in the rest diagnosis was presumptive, based on the clinical picture and investigations (oedema, oliguria and significant proteinuria). Reflux nephropathy was diagnosed by demonstration of a renal scar on ultrasound or intravenous urogram and vesicoureteric reflux on micturating cystourethrogram. All four patients with post-streptococcal glomerulonephritis (PSGN) had clinical setting of the disease, and diagnosis was confirmed by kidney biopsy. The diagnosis of obstructive uropathy was based on intravenous urography and ultrasonographic findings.

Diagnosis of haemolytic–uraemic syndrome (HUS) was based on clinical features, thrombocytopenia, anaemia evidence of haemolysis on peripheral blood smear, such as crenated red cells and/or target cells, schistocytes, and renal histopathology. Likewise the diagnosis of systemic lupus erythematosus (SLE) was based on renal histology and high dsDNA antibody titre, positive antinuclear antibody, and low level of complement C3.

Renovascular hypertension (RVH)

Captopril renogram and intra-arterial digital subtraction angiography was carried out in patients with a high suspicion of renovascular disease (no evidence of renal parenchymal disease, presence of abdominal or peripheral bruit, history of claudication, and constitutional symptoms). The diagnosis of aortoarteritis (AO) was based on the presence of symptoms and signs of ischaemic, inflammatory large-vessel disease as well as classical angiographic findings (multifocal areas of stenosis, irregularity or aneurysm formation of the aorta or its primary branches (or both)). Management of the patient with RVH, in addition to antihypertensive drugs, included revascularization or nephrectomy. Angioplasty is done as a preferred first intervention, as a policy, if the lesion on angiography is amenable to angioplasty. If angioplasty fails, then other options are considered.

In patients with aneurysms, surgical revascularization is considered as a preferred modality. If the kidney size on the affected side was less than 3 cm than the normal side and was contributing to less than 10% of the total function, nephrectomy was considered. Patients who had evidence of active disease were started on prednisolone 1 mg/kg for 3 months, which was tapered to 0.5 mg/kg and ultimately 0.25 mg/kg by the end of 6 months. These patients were regularly followed up for control of blood pressure, and renal function was monitored with 3-monthly serum urea and creatinine and GFR estimation by 99m Tc DTPA scan.

The blood pressure response to intervention was classified as 'cured' if diastolic pressure was normal for the age without medication, 'improved' if diastolic blood pressure was normal for the age but still required drugs, albeit less than those required during pre-revascularization, or 'failed' if any one of above criteria was not met.

Essential hypertension (EH)

The diagnosis of essential hypertension was made after exclusion of relevant secondary causes of hypertension and patients were treated with drugs.

For acute management of accelerated hypertension, nifedipine was given sublingually. Sublingual nifedipine was started with a dose of 0.3 mg/kg; if there was no improvement in blood pressure in 30 min, nifedipine was increased to 0.4 mg/kg and subsequently to 0.6 mg/kg. The patients who failed to respond to three consecutive doses of nifedipine were given intravenous nitroglycerin (10-50 μg/min). Side-effects of drugs were also noted. The patients were followed up 3-monthly for control of blood pressure and renal function.

Results

The common symptoms at presentation were headache (50%), dyspnoea (30%), decreased vision (27.5%), and palpitations (25%) (Figure 1). Twenty-seven patients had grade III, and 13 grade IV, hypertensive changes on fundoscopic examination. The mean systolic and diastolic pressures at presentation were 199 ± 31 and 134 ± 17 mmHg respectively. The mean systolic and diastolic blood pressures in various age groups were higher than the definition given by Second Task Force on Blood Pressure Control in children [12] (Table 1). Twenty-four patients presented with malignant hyper-
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tension as the initial manifestation, and 16 developed malignant hypertension while on antihypertensive drugs. The complications at presentation were renal failure in 23 (mean serum creatinine 396 ± 308 μmol/l), heart failure in 12, and hypertensive encephalopathy in 12. Aetio logically the three main causes of malignant hypertension were renoparenchymal disease (62.5%), renovascular disease (32.5%), and essential hypertension (5%).

Of the renoparenchymal disorders (Table 2) CGN was the most common disease seen in 10 patients (5 had biopsy-proven membranoproliferative glomerulonephritis). Renal failure was present in nine patients and all of them required dialysis during follow-up. One patient had normal renal function at presentation. The mean creatinine at presentation was 500 ± 330 μmol/l. At last follow up, six patients had died, three had received kidney transplant, and one is stable on drugs. Reflux nephropathy was present in five patients of which one received a kidney transplant and the remaining four are stable on drugs. Of the four patients with PSGN, three became normotensive and one required antihypertensive drugs. One patient with obstructive uropathy died of renal failure and the other is stable on antihypertensive drugs. One of the two patients with HUS and the patient with SLE became normotensive. The mean serum creatinine at presentation was significantly higher (P < 0.01) in patients with renal parenchymal diseases (376 ± 316 μmol/l) compared to patients with RVH (96.8 ± 30 μmol/l). Eleven patients with RPD required haemodialysis. Three patients with reflux nephropathy showed improvement in serum creatinine from 161 ± 25 μmol/l to 129 ± 43 μmol/l with control of hypertension.

Renovascular hypertension was present in 13 patients. Eleven had AO and two fibromuscular dysplasia (FMD). In patients of AO, intra-arterial DSA had revealed involvement of the abdominal aorta in 11 (100%), renal-artery stenosis in 11 (100%), subclavian in four (36%), superior mesenteric artery in three (27%), and descending thoracic aorta and coeliac trunk in two each. Carotid and femoral artery involvement was not seen. The renal artery showed bilateral involvement in five, while in six patients it was unilateral (4 left, 2 right). Abdominal aorta showed either mild to moderate stenosis or irregularity of the wall, one patient showed aneurysm in the abdominal aorta in the infrarenal part.

Of the 10 renal arteries in bilateral renal artery stenosis, two were occluded completely, six had stenoses of more than 70%, and in two stenosis was less than 50%. In six unilateral stenoses, two were occluded completely and four had > 70% stenosis.

The mean creatinine at presentation was 96.8 ± 30 μmol/l (Figure 2). Seven of the patients consented for angioplasty (1 FMD, 6 A0). Of the remaining six patients, three had very severe RAS, with the GFR of that kidney contributing to less than 10% of total GFR, and these kidneys were small, not considered for revascularization, and the option of nephrectomy was not accepted by the patients. One patient was lost to follow up and the remaining two did not consent to angioplasty. In those who had angioplasty a check DSA was done, and residual stenosis less than 30% was considered as successful. No follow-up angiography was carried out. Post-angioplasty there was satisfactory dilatation in all seven patients. After a mean follow-up of 15 ± 8 months post-angioplasty, four patients are cured of hypertension, three have partial improvement with a

<table>
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<th>Died</th>
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Fig. 2. Antihypertensives used for maintenance therapy.
The factors for poor control of BP (Table 1) [12]. Three patients with aortoarteritis presented with meningitis-like symptoms (abrupt onset headache, fever, vomiting, and altered mental state). To the best of our knowledge such a presentation of AO has not been reported. Meningitis presenting as hypertension has been reported in the literature [13]; however, our patients had no evidence of meningitis on investigation. CT scan of the head and CSF examination was normal. Sixty per cent of our patients presented with MHT as the initial manifestation. Eight of 11 cases of aortoarteritis had MHT at presentation. In a series of 88 patients by Almeida et al. [14] more than 25% of them presented as malignant hypertension.

The renal parenchymal diseases were the most common cause of malignant hypertension in children, accounting for 62.5% of cases in our series. Various studies on severe hypertension in children have shown that the renal parenchymal diseases account for 59–89%, and the commonest cause is CGN [7–11]. The majority of the patients with RPD had renal impairment at presentation and during follow-up. Eleven patients required dialysis (9 CGN, 1 RN, and 1 obstructive uropathy).

Renovascular hypertension accounts for 5–17% of severe hypertension in children [7–11]. In most of the Asian countries, including ours, aortoarteritis is the most common cause of renovascular hypertension, accounting for about two-thirds of all patients [15]. The reasons for the higher prevalence of AO in India compared to western countries are not known, but could be related to environmental or genetic factors. Tuberculosis was incriminated in earlier studies [16] but has not been confirmed by others [17]. None of our patients had tuberculosis. As AO is prevalent amongst Asians in the USA [18] and is common in Asian countries like Japan and China (HLA A9, A10, B5, DW12 has been shown to be associated with AO in Japanese patients) genetic factors may be playing an important role in its pathogenesis. We have not done HLA typing in our patients. In our study aortoarteritis was the second most common cause of malignant hypertension in children. Renal dysfunction was conspicuously absent in these cases, both at presentation and during follow-up. Hence in children presenting with MHT, the presence of normal renal function is an important clue towards RVH or essential hypertension as the underlying aetiology.
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Percutaneous transluminal angioplasty (PTA) has been an effective first-line procedure in restoring renal vascular flow and in alleviating or facilitating the control of hypertension [19, 20]. PTA has a reported patency rate as high as 80%. Restenosis is the most frequent complication and can occur within 1 to 2 years [18]. In our study revascularization by percutaneous transluminal angioplasty was successful in controlling hypertension. Of seven patients intervened four were off antihypertensive drugs and three had decreased requirement of drugs at a mean follow up of 15 ± 8 months. In a study by Kerr et al. [18], only three of seven PTA that were done for recanalization of the renal artery were successful, and in two cases subsequent bypass procedure was required.

Essential hypertension was present in only 5% of patients of MHT, but this seems to be due to referral selection in our series, as in other studies [7, 8]. Most patients referred to our renal centre present with renal or renovascular disease and not essential hypertension.

The drugs normally used to treat acute hypertension and hypertensive emergencies in the paediatric population include intravenous or intramuscular hydralazine, intravenous diazoxide, sodium nitroprusside, or labetalol [21]. All of these agents require parenteral administration, may cause unacceptable side-effects, especially tachycardia, and require continuous monitoring. Most of these drugs are not easily available in our country. Most centres in our country lack facilities for continuous monitoring of drug delivery and blood pressure. Fortunately sublingual nifedipine in a mean dose of 0.3–0.6 mg/kg was effective in lowering acute severe hypertension in 37 children. The major advantage of nifedipine was its rapid onset of action, and this usually made parenteral drug administration unnecessary. Side-effects were seen on five occasions (4 patients had palpitations and headache, 1 patient developed severe hypotension). Other studies in children have shown it to be effective on each occasion with a duration of action which lasts for 6 h [22, 23]. Since no major adverse effects were encountered and the drug is well tolerated, we prefer this drug to intravenous drugs. Three patients required intravenous nitroglycerin (10–50 µg/min) to control severe hypertension. None of the patients required sodium nitroprusside.

In our series seven patients died, all with renal parenchymal disease as the underlying cause of malignant hypertension (6 CGN and 1 obstructive uropathy). All had advanced renal failure requiring dialysis. They died of uraemia because of the inability to afford renal replacement therapy. The outcome was conspicuously superior in patients with RVH. Of the 23 patients on drug therapy 35% had poor control of blood pressure at last follow-up because of poor compliance related mostly to non-availability of drugs from financial constraints.

Thus we conclude that MHT is not an uncommon problem in our country. Apart from renal parenchymal diseases non-specific aortoarteritis is a common cause of malignant hypertension in children and it commonly presents with MHT as the initial manifestation. Renal function remains normal and percutaneous transluminal angioplasty is an effective method for short-term preservation of renal function and control of hypertension in aortoarteritis. The survival of children with MHT is better in patients with RVH compared to RPD. Sublingual nifedipine is effective and safe for rapid control of severe hypertension.

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