Three patients with arteritis

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SUMMARY Three boys were treated for arteritis of the aorta and great vessels and bilateral renal artery stenosis. One presented at age 6 months with failure to thrive, excessive sweating, and vomiting; hypertension and cardiac failure were subsequently diagnosed. The two older boys (7 and 14 years) presented with symptomless hypertension. The clinical and angiographic findings in the three patients suggest that the illness may have been Takayasu's arteritis, which should be included in the differential diagnosis of hypertension in infancy and childhood. Renal autotransplantation was performed in all three patients with good results. Early renal autotransplantation may reduce the morbidity associated with this disease.

Aortitis with obliterative involvement of the renal arteries and great vessels is a rare disease not always easy to distinguish from the more common causes of widespread vascular disease such as fibromuscular dysplasia or neurofibromatosis. Obliterative arteritis has been termed 'young female arteritis',^{1 2} a 'pulseless disease'³ affecting the aortic arch and either its branches or the descending thoracic and abdominal aorta, or both. Although Takayasu⁴ was the first to describe the ocular manifestations of the disease in a young Japanese woman and it remains most prevalent in Japan, earlier reports of the disease exist,^{5 6} and more recently its occurrence outside Japan has been confirmed.⁷ Takayasu's arteritis is known to occur in childhood,⁸⁻¹⁰ but we report what we believe is the second case of this disease in infancy.¹¹

Treatment has ranged from corticosteroids¹² to endarterectomy,¹³ aortic bypass grafts,^{14 15} and nephrectomy.¹⁶ The more recent surgical technique of renal autotransplantation with or without renal artery reconstruction has been performed in several cases of renovascular hypertension with renal artery stenosis.¹⁷⁻²² There are no long term studies of an infant with Takayasu's arteritis and bilateral renal artery stenosis after bilateral renal autotransplantation.

We report three boys (one an infant) with the likely diagnosis of Takayasu's arteritis and renal artery stenosis seen at this hospital. In all three patients renal autotransplantation has been successful.

Case reports

Case 1. A 6 month old French Canadian infant presented to his general practitioner with failure to thrive, frequent upper respiratory tract infections, and excessive sweating. A 'heart murmur' was noted but no further investigations were done. Five months later he was admitted to a paediatric hospital with cyanotic episodes associated with vomiting and malnutrition.

The infant had been the product of a normal term delivery, and his birthweight was 3.2 kg. His father had a heart murmur that had been investigated by cardiac catheterisation but the diagnosis was not known because he was estranged from the family. There was no family history of neurofibromatosis or café au lait spots. Important clinical findings were height and weight below the third centile, a grade 3/6 ejection systolic murmur over the left sternal edge and the left chest wall, and hypertension, with blood pressure 130/100 mm Hg in arms and legs. Peripheral pulses were full and there was no bruit over the abdomen, back, or neck and no café au lait spots or neurofibromata.

Electrocardiography showed biventricular hypertrophy. Right cardiac catheterisation indicated cardiomegaly secondary to systemic hypertension. An aortogram showed a normal ascending aorta and brachiocephalic artery, and no coarctation or patent ductus arteriosus.

The child was discharged on minoxidil but was readmitted two months later with poor feeding, low

grade fever (38°C), sweating, and vomiting. His blood pressure was 220/140 mm Hg, blood urea nitrogen 8.9 mmol/l, serum creatinine 70 mmol/l, haemoglobin 10.8 g/l, and white blood cells $13.1 \times 10^9/l$ (65% polymorphs, 27% lymphocytes). The erythrocyte sedimentation rate was raised (94 mm/hour). A tuberculin test was negative and serum was negative for rheumatoid factor, antinuclear factor, lupus erythematosus, and venereal disease research laboratory test.

An intravenous pyelogram showed a normal right kidney but delayed nephrogram opacification over the left. An aortogram showed a small left kidney and bilateral renal artery stenosis, more noticeable on the left (Fig. 1). The wall of the abdominal aorta was irregular and there was stenosis of the origin of the coeliac and superior mesenteric arteries. The inferior mesenteric artery was enlarged and there was a large collateral anastomosis between it and the superior mesenteric artery (marginal vessel of Drummond). Plasma renin assay showed consider-

Fig. 1 Case 1—bilateral renal artery stenosis, more noticeable on the left (small arrow).

The left kidney is small. The superior mesenteric artery is stenosed and the marginal artery of Drummond is enlarged (large arrow) signifying marked collateral flow between the superior and inferior mesenteric arteries. The abdominal aorta is enlarged and its wall irregular.

Table Plasma renin values (ng/l/sec)* in the three patients with arteritis

	Inferior vena cava	Right renal vein (RRV)	Left renal vein (LRV)	Ratio of LRV and RRV
Case 1				
At presentation	14.4	14.7	25	> 1.5
After left kidney autotransplantation	8.1	16.7	7.2	> 1.5
Case 2				
At presentation	1.6	1.1	1.4	< 1.5
Case 3				
At presentation	4.9	3.2	20.2	> 1.5

* Normal plasma renin values in our laboratory = <4.2 ng/l/sec in infants and <1.7 ng/l/sec up to 15 years.

able secretion from the left kidney and serious suppression of the right (Table).

The infant was referred to our hospital with intractable hypertension (220/140 mm Hg) and congestive cardiac failure. Left renal autotransplantation with the kidney implanted in the left pelvis and the renal vessels anastomosed to the left common iliac vessels was performed. Despite good perfusion of the autotransplant on differential renal scanning, hypertension persisted and repeat renin studies showed appreciable secretion from the right kidney (Table). Attempted transluminal angioplasty of the right renal artery resulted in complete occlusion of the vessel. On differential renal scanning the left kidney showed 80 to 85% of total renal function. Right renal autotransplantation was underaken, resulting in good perfusion of both kidneys (right kidney 52% and left 48% of total renal function on renal scanning). Four and a half years later the boy remains very well on a small dose of propranolol (5 mg twice daily).

Case 2. A 14 year old, well grown boy of Filipino origin presented to his family practitioner with acne. Blood pressure in both arms and legs was 170/120 mm Hg. He had been normotensive six months previously. Important findings were bilateral renal bruits but full peripheral pulses. There were no bruits over the neck or interscapular region and no café au lait spots or fibromata. The family history did not include hypertension, café au lait spots, or any features suggestive of neurofibromatosis.

The child had had a BCG vaccination and his tine test was positive. The erythrocyte sedimentation rate was 12 mm/hour; urine analysis, complete blood count, serum biochemistry, electrocardiograph, and chest radiograph were normal. Serum was negative for venereal disease research laboratory test, antinuclear factor, and lupus erythematosus. Intravenous pyelogram and the renal scan were

normal. An aortogram and aortic arch angiogram showed a normal aortic arch and vessels but irregularity and abnormal dilation of the abdominal aorta with bilateral renal artery stenosis (Fig. 2). Right and left selective renal angiography showed no intrarenal lesions. The differential renal vein renin values are shown in the Table.

The boy underwent a right renal autotransplant (the kidney was displaced into the right pelvis with an intact ureter looped in an S fashion in the region of the renal hilum). Hypertension persisted after the autotransplant and transluminal angioplasty of the left renal artery was undertaken three months later. His blood pressure was normal for 48 hours after transluminal angioplasty without antihypertensive drugs but then rose to values seen before operation. Twenty months after initial presentation, a left carotid bruit developed and repeat angiography showed extension of the arteritis to the aortic arch and the origins of most of its vessels (Fig. 3). Occlusion of the superior mesenteric artery and stenosis of the left renal artery remained unchanged (Fig. 4).

Case 3. A 7 year old Caucasian boy was noted to have a blood pressure of 160/100 mm Hg in both arms at a routine medical examination. He had been normotensive two years previously. Peripheral

Fig. 3 Case 2—an aortic arch aortogram showing narrowing of the right subclavian artery (large arrow) at the origin of the vertebral artery (which is completely occluded) and noticeable narrowing of the left external carotid artery (small arrow).

Fig. 2 Case 2—bilateral renal artery stenosis (small arrows), irregularity, and abnormal dilation of the abdominal aorta.

The marginal artery of Drummond is prominent (large arrow).

pulses were full and there were no bruits over the abdomen, neck, or back and no café au lait spots. The tuberculin test was negative and the erythrocyte sedimentation rate was 3 mm/hour. Urine analysis, serum biochemistry, complete blood count, serum immunoglobulins, and urine analysis for vanillin mandelic acid and free catecholamines were normal. Serum was negative for antinuclear factor; chest radiograph and intravenous pyelogram were normal. Angiography showed bilateral renal artery stenosis (left more than right), irregularity of the abdominal aorta, complete occlusion of the superior mesenteric artery, enlarged inferior mesenteric artery, and prominent artery of Drummond and collateral vessels. Selective renal angiography showed no evidence that intrarenal vessels were affected. Differential renal vein renins are shown in the Table.

Fig. 4 Case 2—the right autotransplanted kidney in the right iliac fossa (large arrow).

Persistent left renal artery stenosis after transluminal angioplasty is visible (small arrow).

Five months of treatment with prednisone (2 mg/kg/day) did not alter the angiographic appearances and so the child underwent a left renal autotransplant. Six months after surgery, he is well and is normotensive (blood pressure 110/60 mm Hg) on no medication.

Discussion

Takayasu's arteritis is a non-specific arteritis affecting predominantly the aorta and its main branches, with consequent irregularity and narrowing of the aorta, fibrosis, thickening, and stenosis of the juxta-aortic segments of its branches. While the aortic arch is often affected in adults, in children the descending thoracic and abdominal aorta is more commonly affected.^{9 11 23} Aortography shows diffuse narrowing of the aortic arch and descending thoracic or abdominal aorta with juxta-aortic stenoses of the coeliac axis, superior mesenteric artery, renal arteries, and iliac and subclavian vessels.^{17 19 20 22 24} Post-stenotic dilation and aneurysms may occur and collateral circulation is present in over 90% of affected patients. Intrarenal lesions have been described⁸ but artery stenoses usually occur at the origin of the aortic main branches or the bifurcation of the aortic arch vessels.

In our three patients the angiographic findings of

widespread arteritis, narrowing at the origins of arteries, and collateral circulation are consistent with Takayasu's arteritis. Selective renal angiograms in cases 2 and 3 showed no intrarenal lesions. The infant was not subjected to selective renal angiography because of the well recognised difficulties and risks with this procedure in small children.²⁵

The diffuse and extensive involvement of the aorta in Takayasu's arteritis presents angiographic findings similar to atherosclerosis in adults or to syphilitic or tuberculous arteritis. Artery biopsies undertaken in patients with Takayasu's arteritis show non-specific arteritis and help exclude tuberculous, giant cell, and syphilitic arteritis.⁸ We did not undertake such biopsies; we did not consider them essential for diagnosis since there were no clinical or laboratory signs of hypercholesterolaemia, tuberculous, or syphilitic infection and giant cell arteritis occurs more frequently in persons over 50 years of age.

Fibromuscular dysplasia is the most common cause of occlusive renal artery disease and renovascular hypertension in childhood.²⁵ Although it has been described in the renal, carotid,²⁶ coronary,²⁷ and other vessels and progression of the renal artery lesion has been noted,²⁸ symptomatic lesions are usually found in the renal and carotid arteries. Extensive aortitis with irregularity and diffuse narrowing of the aorta is not characteristic of fibromuscular dysplasia,²⁹ which radiographically shows a smooth, fairly focal or tubular concentric narrowing when the orifices of the renal arteries are affected (generally by intimal fibroplasia),^{30 31} or 'chain of beads' appearance when there is medial or subadventitial fibroplasia.²⁸ The angiographic findings in our patients were, therefore, unlike those of fibromuscular dysplasia.

We were also able to exclude neurofibromatosis (von Recklinghausen's disease), a frequent cause of generalised angiodysplasia,²² as the diagnosis. It is generally diagnosed on clinical grounds³² and the absence of café au lait spots, neuroectodermal and mesodermal lesions, or a positive family history,³³ made it an unlikely diagnosis in our patients. Multiple vascular abnormalities including bilateral renal artery stenosis³³ and extensive intracranial arterial occlusive disease³⁴ have been found but there is often intrarenal branch stenosis^{35 36} and angiographic appearance of long segments of smoothly tapered stenosis³⁴—features absent in our three patients.

Since urinary free epinephrine, norepinephrine, metanephrines, and vanillin mandelic acid concentrations were repeatedly normal in the three patients, the diagnosis of pheochromocytoma is also unlikely.

Takayasu's arteritis is uncommon in childhood

and to date there has been only one report of its occurrence in infancy:⁸ a 7 month old child died suddenly with an abdominal mass, hypertension, and congestive cardiac failure; aneurysm of the right common iliac artery and ilio caval fistula secondary to Takayasu's arteritis were found at necropsy. The infant in our study presented at the age of 6 months with vomiting, failure to thrive, excessive sweating, and a heart murmur. His blood pressure was first recorded five months later (170/100 mm Hg) when he presented with the same symptoms, although hospital admission was precipitated by cyanosis associated with vomiting (probably secondary to either aspiration or congestive cardiac failure, or both). Overt cardiac failure was diagnosed soon after confirming the observations made by Gupta *et al*,⁹ who noted incipient or overt cardiac failure in four older children with Takayasu's arteritis.

Hypertension with normal peripheral pulses was common to all three of our patients which suggests that normal pulses do not exclude the diagnosis of Takayasu's arteritis, and confirms Strachan's² observation of a 'pre-pulseless' stage of the disease. Asymptomatic hypertension has been reported in a 2 year old boy with this disorder¹⁰ and also occurred in two of our patients, highlighting the importance of aortography, selective renal angiography, and differential renal vein renin studies³⁷ in evaluating hypertension and surgical considerations.

Differential renal vein renins in cases 1 and 3 showed considerable secretion from the more stenotic renal arteries with appreciable contralateral suppression³⁷ (Table) despite bilateral renal artery stenosis. A two step procedure in case 1, with the more affected kidney autotransplanted first, resulted eventually in good blood pressure control. In case 2 there was no important difference between the left and right renal vein renin values. Selective renal angiography showed no lesion beyond the proximal stenoses of both renal arteries and segmental renin vein sampling was not undertaken. The technique of transluminal angioplasty was not widely used when the patient presented and suitable balloon catheters were not available. A decision for definitive corrective surgery by autotransplanting the right kidney was therefore made.

Hypertension persisted after the operation and transluminal angioplasty of the left renal artery stenosis was performed three months later, using a Gruentzig balloon dilation catheter (FG 7). After dilation, aortography showed improvement in the diameter of the lumen from 4 mm to 5.5 mm (increasing the total cross section area by 100%). Post-stenotic blood pressure in the left renal artery was 58 mm Hg before dilation compared with 78 mm Hg after dilation.

Since the patient's blood pressure fell and remained normal 48 hours after transluminal angioplasty without antihypertensive medication, both this procedure and autotransplantation were probably successful. Although intrarenal lesions are not always found on selective renal angiograms, the fall in blood pressure indicates that the recurring hypertension was not related to such lesions; the subsequent finding of stenosis in the left renal artery suggests this was the more likely cause. Extension of the arteritis to affect the aortic arch and vessels may also have contributed to the hypertension and posed a dilemma to further surgical planning.

In our study transluminal angioplasty failed in case 1 and was only temporarily successful in case 2. The technique was originally refined by Dotter and Judkins³⁸ and subsequently developed by Gruentzig and Kuhlmann.³⁹ It is an alternative to surgery, especially in poor risk patients³⁸ and although some reports^{40, 41} have shown a cure rate of up to 80% in fibromuscular dysplasia and 40 to 70% in patients with atherosclerosis, experience with Takayasu's arteritis is limited as the disease is rare.

Certain lesions are more amenable to dilation than others: fibromuscular dysplasia, short segmental atherosclerotic lesions, and renal orifice lesions respond well to dilation, but with stenosis caused by a large plaque in the abdominal aorta that surrounds the renal orifice the chances of success are diminished.⁴² The results are also not as dramatic in bilateral as in unilateral disease.⁴² A recent report⁴³ of 41 patients who had transluminal angioplasty for renal artery stenosis showed considerable recurrence in two arteries in a one year follow up of five patients with fibromuscular dysplasia who had undergone successful dilation. Of the 17 patients with atherosclerosis, five were 'cured', 10 improved, and two had recurrence of stenosis.

Case 1 is the first report of bilateral renal autotransplantation in a small child with Takayasu's arteritis complicated by renal artery stenosis and hypertension. Surgery controlled his hypertension and cardiac failure and he has been well, with both height and weight greater than the 10th centile (less than the third centile before operation). Renal autotransplantation was first used for high ureteral injuries⁴⁴ but has subsequently been used for renal artery stenosis.^{17, 20, 45, 46} One of the two patients with renal autotransplantation for renovascular hypertension reported by Kaufman *et al*¹⁷ was a 13 year old with middle aorta syndrome who remained normotensive two months after surgery.

Two months of treatment with prednisone in case 3 resulted in no improvement in the arteriography or hypertension. Evidence for successful treatment of Takayasu's arteritis with steroids is inconclusive,¹²

although improvement has been noted in some patients with a raised erythrocyte sedimentation rate.^{47 48}

Despite bilateral renal artery stenosis, renal function was normal in our two young children and only slightly raised in the infant. This confirms the observation by Danaraj and Ong⁴⁹ of prolonged maintenance of renal function in two children who subsequently died without surgery. Recently,⁵⁰ preservation of normal glomerular architecture and recovery of renal function was noted in a 12 year old with Takayasu's arteritis after nine months of haemodialysis. Renal autotransplantation should be undertaken to correct renal artery stenosis and hypertension in Takayasu's arteritis, not because of decline in renal function. A review of 81 patients with Takayasu's arteritis found mortality was highest in the first five years after diagnosis and advocated early surgery for complications.⁵¹

The relation between Takayasu's arteritis and tuberculosis described by several authors^{12 52-54} was not observed in this study. Chest radiographs showed no evidence of past or present tuberculosis and the one patient with a positive tuberculin test had had a BCG. Girls predominate in earlier reports of Takayasu's arteritis^{1 7} and immune mechanisms,⁵² rheumatic aetiology,¹⁴ and B cell alloantigen⁵⁵ have been cited, but the evidence is by no means conclusive.⁵⁶ Our three patients were boys with normal chromosome patterns (46 XY) who had no evidence of immunological disorder.

In conclusion, Takayasu's arteritis should be included in the differential diagnosis of hypertension in infants and children of both sexes. Early renal autotransplantation may reduce the morbidity and mortality associated with this disorder.

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