Severe hypertension after liver transplantation in α_1 antitrypsin deficiency

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Abstract

Five children with α_1 antitrypsin deficiency and terminal liver disease received liver grafts; all five became hypertensive and four developed hypertensive encephalopathy. There was evidence of renal disease pre-operatively and renal biopsy specimens showed variable glomerulonephritic histology with IgA nephropathy in one, mesangial-proliferative changes in two, and mesangio-capillary glomerulonephritis type I in two. Four hypertensive episodes were preceded by a fall in creatinine clearance. The association of glomerulonephritis with α_1 antitrypsin deficiency in children is more common than has been recognised. Affected patients are prone to severe hypertension of probable renal origin after liver transplantation and the renal lesion may affect long term prognosis.

Orthotopic liver transplantation has been used to treat a wide range of potentially lethal liver disorders. In children long term survival rates have gradually improved,^{1 2} but postoperative complications remain frequent and severe, including graft loss and multiorgan failure. Postoperative hypertension is common and usually ascribed to cyclosporin toxicity.³⁻⁶ Among 91 children who received liver transplants in Cambridge between December 1983 and August 1989 postoperative hypertension occurred in 28 (30%) overall. In children with biliary atresia (n=40) the incidence was 22.5% (n=9) and in children with α_1 antitrypsin deficiency (n=14) 71.5% (n=10).

Deficiency of α_1 antitrypsin is associated with liver and lung disease. There is also an infrequently reported association with membranoproliferative glomerulonephritis (new terminology: mesangiocapillary glomerulonephritis type I) usually demonstrated only at necropsy.⁷⁻⁹ The true frequency of renal lesions in these patients is unknown. We report here five children with α_1 antitrypsin who received liver grafts and had perioperative renal biopsies.

Patients and methods

Five patients with α_1 antitrypsin and genotype PiZZ in end stage liver failure received orthotopic liver grafts at Addenbrooke's Hospital, Cambridge, between December 1983 and August 1989. Routine preoperative renal function tests included regular urine analysis and plasma creatinine, urea, and electrolyte estimations. In addition urinary protein loss, creatinine clearance, and glomerular filtration rate were measured in some patients (table). Renal biopsy specimens were obtained during liver transplantation in cases 1, 2, and 4, four weeks postoperatively in case 3, and before the transplant in case 5. Postoperative monitoring included daily 24 hour urine collections for urinary electrolytes and creatinine clearance for the first three to seven days. Serial creatinine clearance measurements are shown in figs 1-5. This method for calculating glomerular filtration rate is accurate in the presence of normal glomerular function but tends to give falsely high values when glomerular function is poor.¹⁰ Relative changes in glomerular filtration rate rather than absolute values are therefore reported and only those plasma creatinine and blood pressure measurements that demonstrated a change from the previous measurement or were abnormal are shown. All blood pressure measurements were taken by the Dinamap non-invasive monitor and the maximum mean arterial pressure of the day was recorded. We have reported only episodes of severe hypertension (mean arterial pressure greater than the 95th centile for age¹¹) which required treatment with antihypertensive agents for at least 48 hours. If there was evidence of associated fluid overload this is indicated in the case descriptions.

The following immunosuppressive regimen was used: intravenous methylprednisolone 10 mg/kg preoperatively and 2 mg/kg/day intravenously or orally from day 1 postoperatively, azathioprine 1.5 mg/kg/day intravenously or orally from day 1, and cyclosporin 1 mg/kg intravenously twice a day (infusion over six hours) on day 2, increased to 2 mg/kg twice a

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Preoperative highest recorded blood pressure measurements and results of hepatic and renal function tests. Normal values are given in parentheses

Case No	Albumin (30-51 g/l)	Prothrombin time (12-16 sec)	Bilirubin (2-17 μ mol/l)	C3 (60-180 mg/100 ml)	Plasma creatinine (27-62 μ mol/l)	Creatinine clearance (90-120 ml/min)	Urinary findings	Blood pressure (mmHg)
1	33	19	46	50	43	317.0	Proteinuria, haematuria	120/80
2	29	20	46	55	61	46.2	Proteinuria 0.3 g/day, haematuria	120/70
3	28	18	37	31	67	—	Proteinuria, haematuria	146/80
4	31	16	23	62	38	66.3	Proteinuria 1.8 g/day, haematuria	120/70
5	20	12	26	57	55	86.0	Proteinuria 2.6 g/day	120/80

Figure 1 Case 1 (age 3.9 years): serial creatinine clearance, blood pressure, and drugs given after transplant.

Figure 2 Case 2 (age 5.7 years): plasma creatinine, serial creatinine clearance, blood pressure, and drugs given after transplant.

Figure 3 Case 3 (age 8.2 years): serial creatinine clearance, blood pressure, and drugs given after transplant.

day from day 3. Trough whole blood cyclosporin concentrations were measured daily by the selective monoclonal antibody based radioimmunoassay (Cyclotrak-SP, Incstar). Episodes of acute rejection were treated with a three day course of intravenous methylprednisolone based on weight (125 mg/day less than 10 kg, 250 mg/day 10–20 kg, and 500 mg/day greater than 20 kg). For persistent and severe rejection a 10 day course of antithymocyte globulin was given.

Results

Salient clinical and laboratory details are shown in the table and figures.

CASE 1

This girl received a liver graft at the age of 3.9 years. Two days before transplantation she was noted to have macroscopic haematuria but she was normotensive. A renal ultrasound scan was normal. An operative renal biopsy specimen showed mild mesangial matriceal increase, thickening of the capillary walls, and intense diffuse staining for IgA, IgG, IgM, C3, and C1q consistent with a diagnosis of IgA nephropathy. Staining for α_1 antitrypsin was negative. On electron microscopy scattered mesangial and paramesangial deposits were identified. On the fifth postoperative day she suffered acute graft rejection unresponsive to methylprednisolone and antithymocyte globulin progressing to liver failure. Before retransplantation she developed severe gastrointestinal bleeding and became hypertensive possibly due to fluid overload. She received a reduced liver graft on the 13th postoperative day. Four days later she became severely hypertensive. She was agitated, confused, and tremulous but there were no seizures. Intravenous cyclosporin was stopped, although plasma concentrations were within the therapeutic range. Despite vigorous treatment with antihypertensive agents her blood pressure could not be controlled effectively. A further episode of acute rejection occurred on the seventh postoperative day, this time successfully treated with methylprednisolone. This was associated with a further rise in blood pressure. Antihypertensives were withdrawn after four weeks. Four months after transplantation she is well and no further episodes of haematuria have been documented.

CASE 2

This boy received a liver graft at the age of 5.7 years. At 5 years of age he had had recurrent episodes of abdominal pain, macroscopic haematuria, and proteinuria. His blood pressure was normal. A renal ultrasound scan demonstrated no abnormality. An operative renal biopsy specimen showed a diffuse glomerulonephritis of mesangiocapillary type I, all the glomeruli showing mesangial hypercellularity and matriceal increase. On the fifth postoperative day he developed acute rejection that was successfully controlled with methylprednisolone. He lost huge volumes of ascitic fluid from the peritoneal drains, however, reaching a maximum of eight litres per day and requiring massive replacement with clotting factors and human albumin. From the 12th day the ascitic fluid was recycled untreated and from the 22nd to the 27th day recycled as an ultrafiltrate. This procedure was well tolerated with normal cardiovascular and respiratory function but with shifts in sodium balance. On day 26 his oral fluid intake was low, his urine output diminished, and the urea rose, indicating early prerenal failure and he had a hypertensive crisis with a maximum blood pressure of

Figure 4 Case 4 (age 8.5 years): serial creatinine clearance, blood pressure, and drugs given after transplant.

Figure 5 Case 5 (age 14.6 years): plasma creatinine, serial creatinine clearance, blood pressure, and drugs given after transplant.

200/150 mm Hg. Despite aggressive treatment with antihypertensive agents he had several grand mal convulsions and episodes of unresponsiveness. Intravenous cyclosporin was stopped, although concentrations were within the therapeutic range. A computed tomogram and examination of his cerebrospinal fluid were normal. By day 31 the blood pressure was controlled but on day 36 he required a laparotomy for biliary peritonitis and postoperatively the blood pressure was again raised and there was evidence of renal impairment with oliguria and a rise in plasma creatinine. Three days postoperatively he had a urinary tract infection associated with haematuria and proteinuria. All antihypertensive agents were stopped 3.5 months after transplantation and urinary protein losses were normal after six months.

CASE 3

This girl received a liver graft at the age of 8.2 years. Three months before transplantation she had deteriorated rapidly with weight loss and increasing ascites requiring regular albumin transfusion. Two episodes of haematuria and proteinuria were observed one year and one week before transplantation and her blood pressure was slightly raised (145/80 mm Hg) a

few days before transplantation. A renal ultrasound scan was normal. Postoperatively she developed severe hypertension. On day 5 her blood pressure reached 200/120 mm Hg and she became unresponsive. A computed tomogram of her head and her cerebrospinal fluid were normal. She developed macroscopic haematuria. Intravenous cyclosporin was stopped, although drug concentrations were within the therapeutic range. On day 6 she became more responsive but had five grand mal convulsions. By day 10 her blood pressure was under control and neurologically she had fully recovered. She then developed severe acute rejection that required three courses of methylprednisolone and one course of antithymocyte globulin for control. Steroid treatment on all three occasions was associated with an increase in blood pressure, haematuria, and heavy proteinuria. Four weeks after transplantation a renal biopsy specimen showed mesangial-proliferative glomerulonephritis with mesangial hypercellularity and diffuse obliteration of epithelial cell foot processes. Staining for IgA was negative and for α_1 antitrypsin positive. The glomerular filtration rate measured at this time was normal (104 ml/min). All antihypertensive agents were stopped six weeks after transplantation. The creatinine clearance was normal seven weeks after transplantation and proteinuria fell to 0.4 g/24 hours at four months.

CASE 4

This boy received a liver graft at the age of 8.5 years. At 7 years he had had his first episode of haematuria and proteinuria but was normotensive. Four months before transplantation he developed severe ascites requiring paracentesis and albumin transfusions. An intraoperative renal biopsy specimen showed mesangiocapillary glomerulonephritis type I with an increase in mesangial cells, mesangial interpositioning, and thickening of the basement membrane. On immunofluorescence there was diffuse, granular deposition of IgM, IgG, IgA, C3, and C1q on glomerular capillary walls. Postoperatively he developed asymptomatic hypertension on day 5 that worsened when high dose steroid treatment was started on day 6 for acute rejection. Cyclosporin concentrations were within the therapeutic range. From day 14 his blood pressure was controlled on oral antihypertensive agents. The creatinine clearance fell to 37 ml/min on day 22 but then increased to normal. Four months after transplantation he was well with a normal blood pressure on treatment with prazosin.

CASE 5

This girl received a liver graft at the age of 14.6 years. At 8 years a severe haemorrhage from oesophageal varices had required an emergency portocaval shunt. At 12 years she had peritonitis caused by *Escherichia coli* and proteinuria was detected. Four weeks before transplantation a renal biopsy specimen taken at another hospital showed a mild mesangialproliferative glomerulo-

nephritis. A renal ultrasound scan demonstrated enlarged kidneys but she was normotensive. The intraoperative course was complicated by bleeding requiring six litres of blood replacement. Over the next 36 hours she continued to bleed, requiring a further six litres of blood, and developed renal impairment with a rising plasma creatinine and urea. On day 3 she became hypertensive and on day 4 developed hypertensive encephalopathy with coma. At that time she had not received any cyclosporin. By day 6 her blood pressure was controlled and she had fully recovered neurologically. On the same day she developed acute rejection and high dose steroid treatment was started during which her blood pressure remained stable. Six weeks after transplantation she had several grand mal convulsions at home. She was found to be hypertensive (blood pressure 170/100 mm Hg) and in renal failure with a plasma creatinine concentration of 128 $\mu\text{mol/l}$ and a urea of 19 mmol/l. She recovered neurologically after vigorous antihypertensive treatment. Unfortunately she died two years later from sepsis and in renal failure while awaiting retransplantation for chronic rejection. Necropsy was not performed.

Discussion

The outcome of liver transplantation has improved progressively in recent years.² Most deaths occur within one month of the operation, the major problems including surgical complications, graft rejection, liver infarction, and infection.³ Some degree of postoperative hypertension is common,³⁻⁵ but it is rarely reported as severe or life threatening. Non-renal causes of hypertension include insufficiently controlled pain or anxiety, water and sodium overload, and drug side effects. Cyclosporin toxicity in particular has been associated with hypertension,⁶ which probably results from direct and indirect vasoconstrictive effects on the afferent glomerular arteriole.¹² The most favoured hypothesis suggests that cyclosporin augments thromboxane A_2 , which produces renal vasoconstriction and also proliferation of vascular smooth muscle cells into the intima. Other renal causes of hypertension include stimulation of the renin-angiotensin system, prostaglandin inhibition, the hepatorenal syndrome, and pre-existing renal disease.

In the Addenbrooke's (Cambridge)/King's College Hospital (London) experience of 91 paediatric liver transplant patients between December 1983 and August 1989 the overall incidence of postoperative hypertension was 30%. The incidence was considerably higher in children with α_1 antitrypsin deficiency (71.5%) than in children with biliary atresia (22.5%) and the degree of hypertension was far more severe, causing hypertensive encephalopathy in four patients, the only patients in the series who developed this complication. The five children with α_1 antitrypsin deficiency described in this study had normal preoperative blood pressures with the exception of case 3 in whom a moderately raised blood pressure was observed once.

Postoperatively all the patients developed

severe hypertension that was difficult to control (figs 1-5). In all except case 2 the onset was between the third and fifth postoperative day. Case 2 lost huge volumes of ascites from the fifth to the 22nd postoperative day and vasoactive substances as well as drugs were probably washed out. Certainly his cyclosporin doses had to be increased significantly and the measured protein content in the ascitic fluid was 50 g/l. All five patients developed acute graft rejection and received between one and three courses (total 13) of high dose steroid treatment. On nine occasions, steroid treatment, including the single dose of methylprednisolone given during the operation, was followed by an appreciable rise in blood pressure which reached its peak between the third and sixth days after the first dose and was associated with an increase in weight and ascites. Antihypertensive treatment often had to be increased during these exacerbations. Four hypertensive episodes were associated with a fall in creatinine clearance, which reached its lowest value either before or on the day of the maximum blood pressure. This suggested that renal arteriolar vasoconstriction may have preceded the onset of hypertension. Renal mechanisms seemed likely to be responsible, probably mediated either by stimulation of the renin-angiotensin system, by augmentation of thromboxane A_2 , or by alteration of renal prostaglandin synthesis after the administration of glucocorticoids.¹³⁻¹⁶ All patients received a large dose of methylprednisolone (10 mg/kg) during the operation, followed by 2 mg/kg/day for 14 days. Suzuki *et al* observed noticeable increases in blood pressure in rats treated with dexamethasone.¹³ The maximum blood pressure was seen between the third and seventh day and decreased after administration of either an angiotensin antagonist or converting enzyme inhibitor. Nasjletti *et al* and Grunfeld *et al* found that glucocorticoids also have a strong depressor effect on basal release of renal prostaglandin, which may contribute to vascular hyper-reactivity in glucocorticoid induced hypertension.^{14 16} Also interesting in the context of this study is the observation of Ramos *et al* that rats with chronic renal failure showed a higher increase in systolic blood pressure after administration of a single dose of methylprednisolone than normal rats.¹⁵ Another aggravating factor may have been reduced clearance of renin and aldosterone due to transiently disturbed hepatic function,¹⁷ but liver function remained satisfactory in these five patients during the periods of hypertension.

Thus many mechanisms may have a role in the development of hypertension after liver transplantation. We have not observed life threatening hypertension, however, in any patient without signs of renal disease. Patients with pre-existing renal disease are likely to be more sensitive to mechanisms which lead to renovascular constriction. Development of either preoperative or postoperative renal failure increases postoperative mortality.¹⁸ In these patients two episodes of postoperative renal failure occurred that were associated with severe hypertensive crises but not related to steroid treatment.

This series of patients suggests that the association of renal disease with the hepatic disease of α_1 antitrypsin deficiency in childhood is more common and more important than has been recognised, especially when such children come to transplantation. The renal disease can easily be overlooked as haematuria and proteinuria may be transient and routine renal function tests are often normal, as seen in our patients. Mean C3 concentrations (51 g/l) were unusually low in comparison with mean prothrombin time (17 sec), both reflecting hepatic synthesis. This suggested possible renal pathology as well as poor hepatic synthetic function.

The pathogenesis of glomerulonephritis in patients with α_1 antitrypsin deficiency remains uncertain. Moroz *et al* found no renal lesions in 16 postmortem examinations on children dying from cirrhosis without α_1 antitrypsin deficiency.⁸ Similarly we have not observed haematuria or proteinuria in children with liver disease not caused by α_1 antitrypsin deficiency. The association between glomerulonephritis and α_1 antitrypsin deficiency thus seems to be more than mere coincidence. Mesangiocapillary glomerulonephritis type I is an immune complex disease clinically characterised by hypocomplementaemia, proteinuria and/or haematuria. The deposition of α_1 antitrypsin has so far only been found in patients with α_1 antitrypsin deficiency and may be specific for this group of patients.⁸ Follow up examination of renal function and symptoms in our patients showed absence of haematuria and proteinuria and normal plasma creatinine concentrations four months after liver transplantation.

In assessing children for liver transplantation knowledge of pre-existing renal disease has important clinical consequences. The onset of hypertension must be anticipated and treated effectively before end organ damage occurs. The antihypertensive agents of first choice in this group of patients may change if future studies confirm raised plasma renin and angiotensin concentrations.¹⁹ Renal function needs to be monitored closely, particularly when nephrotoxic drugs are given. Cyclosporin should be started at low doses and concentrations kept in the lower therapeutic range. Plasma creatinine concentrations can be misleading in the assessment of glomerular function in malnourished patients.¹⁰ Preoperative plasma creatinine measurements were normal in all five patients and postoperatively reached abnormally high concentrations in only two patients, even though glomerular filtration rates measured by creatinine clearance dropped to low concentrations in all five patients.

The prognosis for idiopathic glomerulonephritis type I is serious as end stage renal failure develops in 15–50% of patients within 10 years.²⁰ With IgA nephropathy approximately

10–30% of patients go into end stage renal failure over a period of 20 years. Because of the limited number of cases reported it is unclear if these glomerulonephritides associated with α_1 antitrypsin deficiency have a similar rate of progression. Prospective studies are needed to examine the incidence and prognosis of glomerular abnormalities in liver disease caused by α_1 antitrypsin deficiency and other conditions. Measurement of factors known to have a role in renal hypertension, particularly renin and prostaglandins, may lead to more rational measures for its control. The long term prognosis in α_1 antitrypsin deficient children may be improved by urgent liver grafting once signs of renal involvement have occurred.

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