PAPERS AND SHORT REPORTS

Hypertension in renal allograft recipients may be conveyed by cadaveric kidneys from donors with subarachnoid haemorrhage

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Abstract

Evidence for hypertension was sought retrospectively in the necropsy records of 37 cadaveric kidney donors who had died of subarachnoid haemorrhage and 41 donors who had died of head injury, cerebral tumour, or (in a few instances) other causes. Mean relative heart weight in the donors with subarachnoid haemorrhage was 0.58 (1 SD=0.09)% and in the other donors 0.52 (0.09)% ($p<0.01$), a difference unexplained by any factor other than a comparatively higher blood pressure in the donors who had died of subarachnoid haemorrhage.

Blood pressure was analysed over 72 months after renal transplantation in 23 recipients with normal or near normal graft function and no evidence of chronic rejection or graft artery stenosis. Twelve patients who had received kidneys from donors with subarachnoid haemorrhage had consistently higher systolic blood pressures ($p<0.004$) and needed more antihypertensive treatment ($p<0.0004$) than the 11 recipients of kidneys from donors who had died of head injury or cerebral tumour.

These observations suggest that cadaveric kidneys from donors dying of subarachnoid haemorrhage may induce or sustain hypertension after transplantation.

Introduction

Hypertension in renal transplant recipients may be secondary to chronic rejection, graft artery stenosis, decreased renal function,

weight increase, treatment with corticosteroids, recurrence of the original disease in the graft, and renin secretion from the patient's own kidneys. Occasional reports have suggested that hypertension may in some instances originate from the donor kidney,^{1,2} a finding corroborated by cross transplantation experiments between hypertensive and normotensive rats.³

Patients who die of subarachnoid haemorrhage are a main source of renal allografts, and sometimes they have a history of hypertension. We report a study seeking evidence of hypertension in cardiovascular necropsy data from kidney donors who had died of subarachnoid haemorrhage as compared with donors who had died of head injury or cerebral tumour. A comparison was also made of blood pressures in recipients of kidneys from the two groups of donors.

Materials and methods

Cardiovascular necropsy data were obtained from 78 donors of cadaveric kidneys used in 85 allotransplantations during 1971-82. The clinical course of the recipients was analysed retrospectively by one of us (SS) without knowledge of the donor necropsy data (compiled by UH). We investigated whether the cause of death of the donor influenced the blood pressure of the recipient after transplantation.

Clinical management of allograft recipients—Transplantation was done by a conventional technique, using prednisone and azathioprine for immunosuppression. The best possible matching for HLA-AB and, in later years, DR antigens was attempted in selecting patients. Rejection episodes were diagnosed clinically or by biopsy, as appropriate, and treated with methylprednisolone 3 g intravenously over five days.

Blood pressure and clinical data before and after transplantation—All common causes of chronic renal failure were represented among the patients. Blood pressure was estimated in the uraemic phase before dialysis and again during dialysis, with particular emphasis on the three to six months before transplantation. We also recorded the number of antihypertensive drugs used by each patient. Hypertension was defined as a diastolic blood pressure persistently of 100 mm Hg or higher or a continuing need for antihypertensive treatment, or both.

After transplantation blood pressure, plasma creatinine concentration, number of antihypertensive drugs (including diuretics), doses of prednisone and azathioprine, and body weight were recorded at 3, 6, 9, and 12 months and then yearly for up to 72 months. Diagnoses of graft artery stenosis or chronic rejection were noted, as well as the occasional bilateral nephrectomy for intractable hypertension or severe recurrent infection.

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Results

Of the cadaveric donors, 37 had died of subarachnoid haemorrhage; the remaining 41 had died of head injury or cerebral tumour, or in a few cases had committed suicide (by hanging or poisoning).

The group with subarachnoid haemorrhage comprised 14 men and 23 women with a mean age at death of 45.2 years. The other group of donors comprised 29 men and 12 women with a mean age of 32.8 years. Mean relative heart weights in the two groups (that is, heart weight calculated as percentage of body weight) were 0.58 (1 SD=0.09)% and 0.52 (0.09)% respectively ($p<0.01$; t test and Wilcoxon's test for unpaired data) (fig 1).

FIG 1—Relative heart weights recorded at necropsy in cadaveric kidney donors who had died of subarachnoid haemorrhage or of head injury, cerebral tumour, or suicide. Bars are means and 1 SD. A=All donors ($p<0.01$). B=Donors of kidneys given to recipients with no known cause of hypertension after operation (NS).

Kidneys from 23 donors were given to 23 recipients included in the analysis of post-transplantation blood pressure described below. Of these donors, 12 had died of subarachnoid haemorrhage (five men, seven women; mean age 45.3 years) and 11 of head injury or cerebral tumour (seven men, four women; mean age 38.0 years). Mean relative heart weights in these donors were 0.57 (0.08)% and 0.52 (0.08)% respectively (NS) (fig 1).

Of the 85 recipients of renal allografts, 42 lost the graft or, in a few instances, died within 12 months after transplantation. Of the remaining 43 recipients, 20 were excluded from further analysis because of chronic rejection, graft artery stenosis, effect on hypertension of bilateral nephrectomy, or a plasma creatinine concentration above 150 $\mu\text{mol/l}$ (1.7 mg/100 ml) 12 months after transplantation. Recurrence of the patient's original nephropathy in a graft was not seen. Of the remaining 23 patients, 12 were hypertensive at transplantation.

After transplantation 20 of the 23 recipients were hypertensive. The patients were subdivided into two groups according to the source of the donor kidney. Twelve had received kidneys from donors who had died of subarachnoid haemorrhage and 11 from donors who had died of head injury or cerebral tumour. Table I gives pertinent clinical data on the two groups of recipients; there was no appreciable difference between them in age or sex distribution or cause of renal failure.

Before transplantation blood pressure tended to be higher in the group

TABLE 1—Clinical data on 23 patients at time of transplantation

	Recipients of kidneys from donors with subarachnoid haemorrhage	Recipients of kidneys from donors with head injury or cerebral tumour
No of patients	12	11
Men/women	5/7	8/3
Mean age in years (1 SD)	44.4 (11.8)	37.9 (14.1)
Normotensive at transplantation	7	4
Bilateral nephrectomy	2	1
Cause of chronic renal failure:		
Chronic glomerulonephritis	5	8
Chronic pyelonephritis or interstitial nephritis	3	1
Diabetic nephropathy	1	0
Polycystic kidney disease	1	0
Hypertensive nephrosclerosis	1	1
Uncertain	1	1

who later received kidneys from donors who had died of head injury or cerebral tumour. After transplantation, however, blood pressure fell in these recipients, whereas it increased in recipients of kidneys from donors with subarachnoid haemorrhage. After 12 months the mean blood pressure in these recipients was 158 (1 SD=26)/94 (9) mm Hg and the mean number of antihypertensive drugs taken was 2.0 (1 SD=1.0) (fig 2). In the other group of recipients these figures at 12 months were 139 (10)/90 (7) mm Hg and 1.3 (1.1) respectively. Over the 72 months of observation the blood pressure tended to fall in both groups of recipients, but the difference remained.

Statistical evaluation was carried out as analysis of variance of the arithmetic means of values recorded yearly from 12 to 72 months after transplantation. This confirmed that systolic blood pressure was significantly higher in recipients of kidneys from donors with subarachnoid haemorrhage than in those with kidneys from donors who had died of head

FIG 2—Blood pressure and antihypertensive treatment before dialysis, during dialysis, and after transplantation in 23 kidney transplant recipients with no known cause of postoperative hypertension. Points are means. Vertical bars are 1 SE. ●=Kidneys from donors with head injury or cerebral tumour. ▲=Kidneys from donors with subarachnoid haemorrhage. Significance of differences between treatment groups 12 to 72 months after transplantation: systolic blood pressure $p<0.004$; use of antihypertensive drugs $p<0.0004$. Diastolic pressures were closely similar.

injury or cerebral tumour ($p < 0.004$). Diastolic blood pressure showed no difference between the two groups. More antihypertensive drugs were taken by recipients of kidneys from donors with subarachnoid haemorrhage ($p < 0.0004$). Plasma creatinine concentrations also tended to be higher in this group of recipients than in the other (table II), with overall mean values of $108 \mu\text{mol/l}$ (1.2 mg/100 ml) and $101 \mu\text{mol/l}$ (1.1 mg/100 ml) in the two groups, respectively. This difference was at the limit of significance ($p < 0.04$). No difference was found in the dosage of prednisone between the two groups of recipients. Body weight was higher in recipients of kidneys from donors with head injury or cerebral tumour ($p < 0.002$) (table II).

TABLE II—Plasma creatinine concentrations, prednisone dosage, and body weight in 23 patients with transplants with normal or near normal function and no evidence of chronic rejection or graft artery stenosis. Values are means (1 SD). See text for statistical evaluation

	Months after transplantation						
	3	12	24	36	48	60	72
<i>Recipients of kidneys from donors with subarachnoid haemorrhage</i>							
Plasma creatinine ($\mu\text{mol/l}$)	109 (22)	112 (20)	111 (26)	108 (28)	112 (19)	108 (23)	99 (18)
Prednisone dosage (mg/day)	22.0 (6.3)	15.5 (3.5)	12.8 (2.9)	10.7 (2.4)	9.6 (1.7)	9.6 (1.7)	9.5 (1.1)
Body weight (kg)	61.9 (9.3)	61.8 (8.5)	64.4 (10.1)	64.7 (12.4)	66.5 (11.6)	67.0 (13.3)	61.3 (7.9)
No of observations	12	12	10	9	8	7	5
<i>Recipients of kidneys from donors with head injury or cerebral tumour</i>							
Plasma creatinine ($\mu\text{mol/l}$)	110 (35)	107 (28)	102 (23)	107 (25)	95 (28)	100 (21)	94 (25)
Prednisone dosage (mg/day)	21.9 (1.8)	16.8 (1.9)	12.8 (2.5)	11.5 (2.9)	9.1 (2.0)	7.1 (4.3)	5.5 (4.1)
Body weight (kg)	68.7 (10.8)	74.6 (14.6)	74.0 (16.1)	67.5 (11.4)	67.4 (11.4)	73.6 (17.7)	71.0 (17.8)
No of observations	11	11	11	8	7	6	5

Conversion: SI to traditional units—Plasma creatinine: $1 \mu\text{mol/l} \approx 0.01 \text{ mg/100 ml}$.

Blood pressures before transplantation had no influence on the average blood pressures after transplantation or the number of antihypertensive drugs used.

Discussion

Hypertrophy of the heart as recorded at necropsy may be due to several factors, including hypertension. Others are heart failure, valvular heart disease, hypertrophic cardiomyopathy, obesity, and a sustained high level of physical exercise. The necropsy records of the cadaveric kidney donors in this study contained no information about heart disease, which, if clinically important, would have precluded kidney donation. Obese patients have hypertrophied hearts but a relative heart weight similar to that of non-obese subjects.⁴

Relative heart weight would be disproportionately influenced by acute weight loss during the donor's terminal illness. Such weight loss, due to increased catabolism or dehydration, cannot be evaluated in a retrospective study but would be expected to affect patients with subarachnoid haemorrhage and head injury or cerebral tumour to the same extent. "Sport heart" hypertrophy would be expected to be more frequent among the predominantly young men with head injury, and the predominance of women among the donors with subarachnoid haemorrhage would tend to decrease average relative heart weight in that group.⁵ Both of these factors operate against the difference in relative heart weight found between the two groups of donors, and we conclude that higher blood pressure in the donors dying of subarachnoid haemorrhage was the more likely explanation for the heart hypertrophy found at necropsy.

From neurosurgical studies hypertension is known to be present with increased frequency in patients with subarachnoid haemorrhage, though its exact prevalence is uncertain.⁶ Hypertensive disease in these patients may originate in the kidneys or cause secondary discrete renal changes, in either case making possible the transfer of hypertension from kidney donors to recipients.

Post-transplantation hypertension—defined as a diastolic blood pressure persistently of 100 mm Hg or higher or a continuing need for antihypertensive treatment, or both—was present in 20 of our 23 transplant recipients; only 12 patients had been hypertensive before

operation. The prevalence of hypertension among patients with transplants plainly depends on how high blood pressure is defined. Thus a study in which the hypertensive limit was a diastolic pressure of 110 mm Hg or more found that one fifth of patients were hypertensive.⁷ A Belgian study using the same definition of hypertension as in our study and conducted over 11 years found hypertension in 65% of patients with transplants whose own kidneys were in situ as compared with only half of patients whose own kidneys had been removed.^{8,9} The authors concluded that in

around 15% of cases hypertension after transplantation could be ascribed to the patients' own kidneys. The nature of the original kidney disease did not influence blood pressure after transplantation.⁹ By contrast, Tejani found hypertension in 87% of children with transplants, with more severe rises in pressure in those with nephritic as opposed to "structural" kidney disease.¹⁰

Before our study only a few reports had hinted at a "donor factor" in hypertension after renal allotransplantation. McDonald *et al* transplanted kidneys from a donor with hepatorenal syndrome into two anephric patients. These kidneys (with a high content of renin) were therefore transplanted into a milieu with a high concentration of circulating renin substrate: severe transient hypertension occurred immediately.¹ Merino *et al* compared 11 normotensive with 11 hypertensive recipients of kidneys from living related donors and found a predominance of hypertension among the donors in the latter group.²

In a study with rats Bianchi *et al* found that hypertension could be cured or induced by cross transplantation of kidneys between normotensive and spontaneously hypertensive rats of the Milan strain, the animals undergoing bilateral nephrectomy at the time of transplantation.³ In a related study in patients with essential hypertension and nephrosclerosis normotension prevailed after bilateral nephrectomy and transplantation of kidneys from putatively normotensive donors.¹¹ It has also been shown that hypertension in the parents of cadaveric kidney donors is associated with a significant increase in blood pressure in recipients.¹²

In our study patients who were given kidneys from donors who had died of subarachnoid haemorrhage and who showed no sign of chronic rejection or graft artery stenosis and retained normal or near normal renal function remained noticeably hypertensive over the six years of observation. By contrast, patients given cadaveric kidneys from donors with head injury or cerebral tumour had lower blood pressures and less need of antihypertensive drugs after operation and might be considered to have been partially "cured" of their hypertension. The necropsy data strongly suggest that the donors who died of subarachnoid haemorrhage had had comparatively high blood pressures before their fatal illness. Thus clinical renal allotransplantation with cadaveric kidneys bears some similarity to the cross transplantation experiments of Bianchi *et al* in hypertensive and normotensive rats. Transplanted kidneys that convey hypertension to the recipient may also contribute a risk factor,

though this would be expected to be balanced by effective anti-hypertensive treatment.

Necropsy reports on some of the cadaveric kidney donors were kindly provided by the departments of pathology at the following hospitals: Hvidovre Hospital; the State University Hospital of Copenhagen; Bispebjerg Hospital; Odense Hospital; Århus Municipal Hospital; and Esbjerg Hospital; and the Institute of Forensic Medicine at the University of Copenhagen, Denmark. Clinical data on some of the transplant recipients were kindly provided by the departments of nephrology at Hvidovre Hospital, Odense Hospital, Århus Municipal Hospital, and Ålborg Hospital South, Denmark. Dr Birger Broch Møller gave valuable advice on the statistical handling of the data.

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Antibody response and clinical reactions in children given measles vaccine with immunoglobulin

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Abstract

Antibody responses and clinical reactions to three measles vaccines (Attenuvax, Mevilin, and Rimevax) injected into the opposite arm to immunoglobulin were assessed in 45 children with brain disorders making them susceptible to fits if given measles vaccine alone.

In this small study no unacceptable reactions occurred and in only three cases was the antibody response minimal or absent.

More children in this special category should be considered for vaccination against measles in this way.

Introduction

When measles vaccine was licensed in the United States in 1963 the only live vaccine available was the Enders Edmonston B strain, which produced unacceptable clinical reactions in up to 60% of children. With the aim of reducing these reactions standardised measles immunoglobulin was given at the same time in a different site. Though the antibody response was slightly reduced it nevertheless persisted for up to three years.¹ Between 1963 and 1965 in the United States some 5 million doses of Edmonston B vaccine were distributed each year with the official recommendation that immunoglobulin should be given simultaneously.

The antibody response to vaccines given with small doses of immunoglobulin was reported in Britain in 1964.² The three vaccines were Edmonston B, Edmonston A after 65 further passages, and Edmonston B after 30 passages. The conclusion was that the reactions were mild and the antibody response satisfactory when these vaccines were given with immunoglobulin but that the vaccines were not suitable for use alone.

At present in Britain three further attenuated vaccines are in use: Mevilin (Evans Medical), Rimevax (Smith Kline and French), and Attenuvax (Merck Sharp and Dohme) (fig 1). Concurrent immunoglobulin is now recommended by the Department of Health only for children with a personal history of convulsions or a close family history of non-traumatic epilepsy.³ We have assessed the antibody responses and clinical reactions to current measles vaccines given with immunoglobulin in children in whom measles vaccine alone was contraindicated.

FIG 1—Derivation of measles vaccines (measles virus isolated from Edmonston strain by Enders).

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Subjects and methods

Forty five children aged between 1 and 3 years were included in the study, 19 at The Hospital for Sick Children, Great Ormond Street, London, and 26 at the Immunisation Advisory Clinic, Barking. All had a history of convulsions, fits in the neonatal period, or other relevant neurological disorders. Twelve received Attenuvax, seven Mevilin, and 26 Rimevax. Serum samples were taken before vaccination and not less than eight weeks after vaccination. The recommended dose of normal immunoglobulin