$\varkappa=1$ indicates perfect consistency and $\varkappa\leq 0$ complete inconsistency.

When a gold standard is present the validity of every reviewer can be studied. The observed validity (OV)—that is, the proportion of correct diagnoses—must be compared with the chance validity (CV), where CV=(EP)(P)+(1−EP)(1−P) and P is the real prevalence. When EP=P, $CV=2(EP-0{\cdot}5)^2+0{\cdot}5$.

A simple overall measure for diagnostic validity is (OV−CV):(1−CV). Because validity is more important than consistency it is named iota (I), one letter before kappa in the Greek alphabet. Iota among patients with disease is I(sensitivity)=(OSE−EP):(1−EP), in which OSE stands for the observed sensitivity. Iota among those without disease is I(specificity)=(OSP−(1−EP)):(1−(1−EP)), in which OSP stands for the observed specificity. I=1 indicates perfect validity and I≤0 no validity at all beyond chance validity.

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Aluminium accumulation and immunosuppressive effect in recipients of kidney transplants

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Abstract

Aluminium that has accumulated in the body is thought to have a generalised cytotoxic effect. A prospective study of aluminium accumulation in bone—that is, subclinical aluminium toxicity—was carried out in 94 recipients of kidney allografts, who were followed up for three years. Subclinical aluminium toxicity was found in 66 patients. A significantly smaller proportion of patients with aluminium accumulation experienced a rejection episode: 30 (58%) *v* 12 (86%) who received grafts from cadavers and 4 (29%) *v* 10 (71%) who received grafts from living donors. On multivariate analysis only the source of the kidney and aluminium accumulation were found to influence the rejection rate.

These findings suggest that aluminium accumulation has an immunosuppressive effect.

Introduction

Aluminium accumulation is a potential hazard of end stage chronic renal failure.[1,2] Aluminium toxicity is indicated by the accumulation of aluminium in bone and by symptoms and signs from several organs.[3,4] The biochemical basis of aluminium toxicity is complex,[5] but the diverse clinical pictures suggest a generalised cytotoxic effect.[4] Its influence on immune function remains to be elucidated. We report a prospective study of aluminium accumulation in recipients of kidney transplants and its relation to immune events after transplantation.

Patients and methods

We studied 94 adult patients, who gave their informed consent to participate and received a kidney graft from a cadaver (n=66) or a living donor identical for histocompatibility antigens (n=28) during one year (1983-4). They represented 83% of all patients eligible for study. Patients who received a cadaveric transplant were selected on the basis of medical urgency, waiting time, and a negative result of a cross matching test against donor T cells. Blood transfusions were given for medical reasons only. The patients' immune systems were suppressed by a uniform regimen that included cyclosporin and steroids.[6] Rejection episodes were treated by intravenous bolus doses of methylprednisolone.[6] All patients were followed up for three years.

Rejection episodes were defined by a rise in serum creatinine concentration not explained by non-immunological complications as shown by renography, sonography, computed tomography, monitoring of cyclosporin concentrations, and intravenous pyelography or angiography; improved renal function after treatment for rejection; or results of renal biopsy. Non-functioning grafts were monitored by fine needle aspiration cytology.

Randomly chosen sections of a specimen of transiliac bone obtained during the transplant operation were stained with aurin tricarboxylic acid and Prussian blue. Aluminium accumulation was said to be present if the aurin tricarboxylic acid stain was positive[7] and the Prussian blue stain negative. Histochemical staining for aluminium is usually negative unless the aluminium content in bone exceeds 50 mg/kg dry weight (10 times the normal concentration).[8]

Wilcoxon two sample tests and Fisher's exact tests were used to test differences between groups. One sided Fisher's exact tests were used as aluminium is known to have toxic effects only in biological systems. Log rank tests were used to test differences in survival rates. Multivariate analyses were performed to test simultaneously the influence on the rejection rate of several factors existing before transplantation. This was done with a logistic model and generalised linear interactive modelling[9]—that is, a logit analysis as all covariates were categorised.

Results

Aluminium accumulation was found in 52 (79%) patients who received kidneys from cadavers and 14 (50%) patients who received kidneys from living donors (table I). Age, histocompatibility matching, and the proportion of patients previously given transfusions or dialysis were similar in patients positive and negative for aluminium.

One and three year survival rates of patients were 89% and 76% for recipients of kidneys from cadavers and 100% for recipients of kidneys from living donors, with no difference between groups of patients positive and negative for aluminium. One and three year survival rates of grafts were 73% and 62% for kidneys from cadavers and 96% and 82% for kidneys from living donors. Patients positive for aluminium tended to have better graft survival than patients negative for aluminium, but the difference was not significant.

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TABLE I—*Aluminium accumulation before kidney transplantation and age of patients, histocompatibility of graft, prevalence of transfusion and dialysis before transplantation, graft survival, and occurrence of rejection episodes according to whether kidney was from a cadaver or living donor*

	Kidney from cadaver		Kidney from living donor	
	Aluminium staining positive (n=52)	Aluminium staining negative (n=14)	Aluminium staining positive (n=14)	Aluminium staining negative (n=14)
Mean age (years)	50·4	50·2	27·4	32·1
Mean No of HLA-A or B mismatches	2·4	2·5	1·9	1·4
Mean No of HLA-DR mismatches	1·0	0·8	0·8	0·6
No (%) of patients given blood transfusion	45 (87)	8 (57)	12 (86]	8 (57)
No (%) of patients given dialysis	47 (90)	10 (71)	12 (86)	8 (57)
No (%) of grafts surviving at one year	40 (77)	8 (57)	14 (100)	13 (93)
No (%) of grafts surviving at three years	33 (63)	8 (57)	13 (93)	10 (71)
No (%) of patients who had rejection episode(s) in first year after transplantation	30 (58)*	12 (86)	4 (29)**	10 (71)

*p=0·048; **p=0·029.

TABLE II—*Deviance between observed and estimated rejection rates in multivariate analyses*

Variables included in model*	Deviance	Degrees of freedom
Donor + aluminium + dialysis + transfusion	13·52	10
Donor + aluminium + transfusion	13·57	11
Donor + aluminium	14·48	12
Donor + dialysis + transfusion	20·45	11

*Cadaver or living donor; aluminium accumulation present or absent; dialysis given before transplantation or not given; transfusion given before transplantation or not given.

Graft rejection was the main cause of early graft loss, causing 14 of the 19 losses during the first year.

A rejection episode occurred during the first year in 42 (63%) patients who received kidneys from cadavers and 14 (50%) who received kidneys from living donors. A significantly smaller proportion of patients positive than negative for aluminium had a rejection episode: 30 (58%) *v* 12 (86%) recipients of grafts from cadavers (p=0·048) and 4 (29%) *v* 10 (71%) recipients of grafts from living donors (p=0·029). The rejection rate was not associated with age, histocompatibility matching, blood transfusions before transplantation, or dialysis.

An acceptable deviance between observed and estimated rejection rates was found by multivariate analysis of several models that included various combinations of variables (table II). An acceptable fit relative to the degree of freedom was observed in a model that included only the donor source and aluminium accumulation, whereas the model that did not take aluminium accumulation into account fitted poorly.

The risk of rejection of a graft from a cadaver was 3·2 times higher than the risk of rejection of a graft from a living donor (95% confidence interval 1·1 to 9·5), whereas the odds ratio was 0·2 (0·1 to 0·7) when comparing survival of grafts in patients positive and negative for aluminium. Neither dialysis nor transfusion influenced the rejection rate (odds ratio for dialysis 0·9 (0·2 to 3·2), for transfusion 0·6 (0·2 to 2·0)).

Discussion

Our study confirms previous reports of a high prevalence of aluminium accumulation in patients with end stage renal failure.[10 11] To our knowledge this is the first report of aluminium accumulation and the clinical course after transplantation.

Rejection episodes occurred less commonly in patients with aluminium accumulation irrespective of age, histocompatibility matching, and transfusion and dialysis state before transplantation. These findings are compatible with a hypothesis that subclinical and clinical aluminium toxicity suppresses the alloimmune response.

Although a lower rejection rate in patients with aluminium accumulation did not result in significantly improved survival of grafts in our small series, a differential prevalence of aluminium accumulation in various subgroups may confound analysis of factors influencing prognosis in large populations. For example, blood transfusions before transplantation were found in most studies during the 1970s and early 1980s to enhance survival of grafts,[12-15] but the effect was never clearly understood and seems to have vanished in recent years.[6 15 16] During the 1980s aluminium toxicity has been greatly reduced in patients with end stage renal failure after correction of its main causes—namely, contamination of the dialysis fluid with aluminium and use of phosphate binders containing aluminium.[17 18] Prolonged treatment by dialysis increases the risk of aluminium accumulation,[19] patients receiving dialysis require more transfusions, and sensitisation induced by transfusion prolongs the waiting (and dialysis) time before transplantation.[13] Thus we propose that some of the controversies regarding the influence on prognosis of transfusions and dialysis before transplantation can be explained by the immunosuppressive effect of aluminium accumulation.

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