SHORT REPORTS

Parathyroid hormone as a causative factor of primary non-function in renal transplants

Primary non-function of renal allografts, which continues to be a common early problem in transplantation, can be diagnosed when rejection and vascular problems have been excluded and biopsy findings are compatible with acute tubular necrosis. Early studies have defined factors affecting the donor kidney which are associated with primary non-function, and these include prolonged warm and cold ischaemia times.¹ We sought to examine whether any non-immunological recipient factors play a part in primary non-function. There is substantial evidence that increased influx of calcium into the cell plays a role in cellular toxicity.² Recent studies have suggested that parathyroid hormone causes increased levels of cytosolic calcium.³ The aim of this study was to review the immunoassayable parathyroid hormone (C terminal) concentrations immediately before transplantation in patients receiving a cadaveric renal transplant and their relation to the incidence of primary non-function.

Methods and results

We performed a retrospective analysis of 52 patients who underwent cadaveric renal transplantation during 1983-5 at this centre. The group included 27 men and 25 women aged 10 to 62 years. Twenty seven patients were undergoing haemodialysis and 25 chronic ambulatory peritoneal dialysis before transplantation. Forty five patients received their first transplant and seven their second or third transplant. Immunosuppression comprised prednisolone, 0.3 mg/kg body weight, and cyclosporin in doses tailored to maintain plasma trough concentrations at 50-150 µg/l as measured by high pressure liquid chromatography. Blood was taken immediately before transplantation for measuring total calcium, phosphate, and C terminal immunoassayable parathyroid hormone concentrations.

The patients were divided into two groups according to whether their renal graft functioned immediately after transplantation or not. Primary non-function was diagnosed in those patients who required renal replacement treatment immediately after transplantation in the absence of rejection or a vascular cause.

Mean (SEM) plasma calcium, phosphate, and immunoassayable parathyroid hormone concentrations before transplantation in renal allografts showing primary function and primary non-function

	Plasma calcium (mmol/l)	Plasma phosphate (mmol/l)	i-PTH (ng/l) (normal range <1200)	Cold ischaemia time (h)
Primary function	2.50 (0.04)	1.64 (0.09)	1760 (330)	20.8 (2)
Primary non-function	2.56 (0.04)	1.78 (0.10)	3069 (389)	21.5 (2)
p Value	NS	NS	<0.01	NS

*Unpaired t test.
i-PTH=Immunoassayable parathyroid hormone.

Twenty four patients within this period had primary non-function as defined. There were no differences in cyclosporin concentrations or HLA matching between these groups. The table shows that the primary non-function group had significantly higher parathyroid hormone concentrations, although the cold ischaemia time and total plasma calcium and phosphate values were not significantly different.

Comment

Parathyroid hormone has been postulated as a potential uraemic toxin, and recent studies have shown that it can cause an increase in proximal cell membrane calcium permeability,⁴ possibly through a similar mechanism to the calcium channels activated by parathyroid hormone that are found in an osteosarcoma cell line.⁵ These data would be compatible with the hypothesis that parathyroid hormone may have a nephrotoxic effect on the renal transplant. Parathyroid hormone concentration thus represents the first non-immunological recipient factor shown to affect primary non-function in the graft.

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(Accepted 1 October 1987)

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Use of acyclovir to treat chickenpox in pregnancy

Varicella, usually a fairly benign disease, may be severe and fatal—for example, in the immunosuppressed and in pregnancy.¹ The only death from chickenpox in an adult admitted to this regional infectious diseases unit between 1984 and 1987 occurred in a pregnant woman. We describe this case together with three other cases of chickenpox in pregnancy in otherwise healthy women, all of whom were treated with intravenous acyclovir. A recent report suggests an association between smoking and varicella pneumonia.² All four of our patients were smokers; three had pneumonia.

Case reports

Case 1—A 33 year old woman, 26 weeks pregnant, presented on the fourth day of illness with dyspnoea. She was feverish with a mild typical varicella rash. Despite minimal chest signs radiography showed widespread pneumonitis. Treatment with acyclovir (5 mg/kg eight hourly) stopped the development of skin lesions, but increasing hypoxia necessitated ventilation. The baby, delivered by caesarean section, died shortly after birth. Despite slow improvement in respiratory function the mother died a month later after an emergency laparotomy for intestinal obstruction. No necropsy was permitted.

Case 2—A 22 year old woman, 25 weeks pregnant, presented with cough and dyspnoea at rest one day after the appearance of a chickenpox rash. She had minimal chest signs, hypoxia, and bilateral pneumonitis as shown by radiography. She received treatment with acyclovir (10 mg/kg eight hourly). The following day, despite oxygen treatment, she was more hypoxic and the dosage of acyclovir was increased to 18 mg/kg eight hourly with a good response. This was maintained for six days without apparent side effects. Despite transient premature labour pregnancy continued, and a normal baby was delivered at term.

Case 3—A 27 year old woman, 28 weeks pregnant, presented with a 24 hour history of dyspnoea on exertion six days after the onset of chickenpox. She had a widespread rash, with new vesicles still developing, and radiography showed extensive pulmonary damage. She was very hypoxic. Five days of treatment with acyclovir (15 mg/kg eight hourly) produced rapid improvement. Pregnancy proceeded, with term delivery of a normal baby.

Case 4—A 20 year old woman presented at 38 weeks' gestation with the early stages of a varicella rash. There were no respiratory symptoms, and chest radiographs were normal. After five days of treatment with acyclovir (10 mg/kg eight hourly) her rash resolved rapidly. A healthy infant with no evidence of infection was delivered by caesarean section (breech presentation) eight days later.

Comment

In our patients there was little correlation between the severity of rash and life threatening disease. The consistent pointer to pneumonitis was tachypnoea. Varicella zoster immunoglobulin is about 50% effective in preventing chickenpox in susceptible contacts (trials have been carried out in the non-pregnant) or in modifying its course.³ It had not been given in the patients described despite all having histories of domestic contact.

The data sheet for acyclovir currently recommends 5 mg/kg eight hourly for normal patients and 10 mg/kg for those who are immunocompromised. After our experience with the first patient the second and third were given a higher dose. The fourth patient may have avoided pneumonitis through its early use. Varicella zoster is known to be less sensitive than herpes simplex virus. Reversible impairment of renal function is the most important adverse effect, resulting from renal deposition when hydration or renal function is inadequate. Acyclovir should be infused slowly with a litre of fluid for each gram of the drug.⁴ Animal studies have not shown adverse effects from acyclovir on the fetus, and treatment of disseminated herpes simplex in pregnancy in humans has been reported with no apparent fetal damage.⁵

Our experience suggests that chickenpox in pregnancy is sufficiently hazardous to merit admission to hospital and early treatment with acyclovir, especially if pulmonary damage is suspected. Possible harmful effects to the fetus must be considered but do not seem to have occurred in our patients, who received treatment in the second and third trimesters.

We thank Dr I W Pinkerton of Ruchill Hospital and Dr W P Black of the Royal Maternity Hospital, Glasgow, for permission to study their patients and to Mr J K Roberts of Wellcome Foundation for his advice on the use of acyclovir in pregnancy.

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(Accepted 8 October 1987)

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Failure of salt to increase starch digestibility and glycaemic response

The hypothesis that dietary starch is digested more rapidly when it is taken together with salt is plausible but rests only on a report that six normal subjects tended to have higher plasma glucose or insulin concentrations when they breakfasted on lentils or bread with added salt.¹ Another small study found no difference in glycaemia when salt was added to glucose or macaroni test meals.² We tested this hypothesis in a larger group of subjects, measuring insulin as well as glucose responses and also estimating the escape of undigested starch from the small intestine. The test meal was designed to be a realistic, mixed meal.

Subjects, methods, and results

Thirteen healthy non-obese volunteers (aged 20-69) took part in the study. Four were male medical students and nine (four men) had normally functioning ileostomies after a curative colectomy for ulcerative colitis performed at least one year beforehand. No subject was taking any medication.

Test meals (52.4 g carbohydrate, 17.1 g protein, 17.1 g fat) consisted of 21 g Cheddar cheese, 8 g butter, 300 ml tea, 50 g milk, and a baked wholewheat bread scone containing 50 g carbohydrate. The scones consisted of 76 g finely ground wholewheat flour, 0.75 g sodium bicarbonate, 1.5 g cream of tartar, and 50 g water; the salted scones contained in addition 4.25 g of sodium chloride. The total sodium contents of the salted and unsalted meals were 87 mmol and 16 mmol respectively. All the scones were baked undisturbed at 210°C for 15 minutes in the same oven. After baking they were cooled then stored at -18°C. When required they were thawed overnight.

After a 12 hour overnight fast venous blood samples were taken in the fasting state and 10, 20, 30, 40, 50, 60, 75, 90, 120, and 180 minutes after the test meal (except in one subject with an ileostomy in whom venous access was not possible). Ileostomy effluent was collected in hourly samples for eight hours after the test meal and immediately stored at -20°C until the time of assay. Test meals were administered in random order and were consumed steadily over 20 minutes under supervision. Plasma glucose concentrations were measured in an autoanalyser by the glucose oxidase method. Plasma insulin was estimated by radioimmunoassay.³ Starch in the homogenised ileostomy effluent was measured as the glucose

released during incubation with amyloglucosidase.⁴ Areas under the insulin and glucose concentration curves were estimated as those above the zero time point. Student's paired *t* test was used in comparing the response to the salted and unsalted meals. Results are expressed as means (and standard errors). The study was approved by the Bristol and Weston health district ethical committee.

The meals containing unsalted and salted bread produced no significant differences in plasma glucose concentration at any postprandial time point or in area under the glucose concentration curve (table). In addition neither individual postprandial plasma insulin values nor area under the insulin concentration curve differed significantly between the two meals (table). If it had any effect, salt tended to reduce the metabolic response to starch.

Plasma glucose and insulin responses to mixed meals based on bread with and without added salt in 12 subjects. Results are means (and standard errors)

	No salt	Salt
Fasting glucose (mmol/l)	3.85 (0.15)	3.97 (0.14)
Peak glucose (mmol/l)	5.95 (0.26)	5.90 (0.20)
Area under glucose curve (mmol/l min)	145 (22)	105 (17)
Fasting insulin (mU/l)	5.00 (1.00)	6.00 (1.00)
Peak insulin (mU/l)	49 (5)	49 (6)
Area under insulin curve (mU/l min)	3728 (411)	3059 (287)

Comment

These findings make it unlikely that salt increases the rate of starch digestion to any important extent, at least in the context of a normal mixed meal.

Starch output in the subjects who had had ileostomies tended to be higher after the meals containing salted bread, not lower as predicted by the hypothesis, but this difference was not significant (502 (216) mg glucose *v* 397 (164) mg glucose, *n*=9). Clearly, salt does not reduce the physiological malabsorption of starch which occurs in healthy subjects.^{4,5} This again makes it unlikely that salt affects starch digestion to an important extent in real life. In the light of these data, salt restriction is unlikely to help control postprandial glycaemia in diabetics.¹

We thank Miss A Moffatt and the chemical pathology laboratory, Bristol Royal Infirmary, for their expert technical help. The study was supported by the Bristol and Weston Health Authority.

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(Accepted 6 October 1987)

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Cholesterol embolism in a renal graft after treatment with streptokinase

The clinical features of cholesterol embolism in the kidney have been well delineated.¹ We report a case of acute renal graft failure due to cholesterol emboli. We further suggest that fibrinolytic treatment caused the disease and draw attention to this potential complication of an increasingly popular treatment of myocardial infarction.^{2,3}

Case report

A 56 year old man was admitted to hospital with chest pain that had lasted four hours. Nineteen years earlier he had received a cadaver kidney transplant after a 20 year history of chronic glomerulonephritis with hypertension. No rejection occurred. Serum creatinine concentration was stable at 150 µmol/l. Maintenance