SHORT REPORTS

Pregnancy after renal transplantation: severe intrauterine growth retardation during treatment with cyclosporin A

Cyclosporin A is a fungal metabolite whose inhibitory effect is on T lymphocytes and in particular on cells mediating rejection of allografts. Evidence suggests that it may be more effective than conventional immunosuppressive treatment in recipients of organ transplants.[1] Successful pregnancies have been reported in allograft recipients receiving cyclosporin daily from conception to delivery.[2,3] We describe the clinical course of a pregnancy in a renal allograft recipient receiving cyclosporin A in which the fetus was growth retarded; we also review other such pregnancies.

Case report

A 31 year old woman underwent successful renal transplantation in 1983 for chronic renal failure secondary to malignant hypertension. Before developing renal failure she had had two normal normotensive pregnancies, which had resulted in two infants born at term weighing 2750 g and 2700 g. After developing severe hypertension and renal failure she conceived twice while receiving haemodialysis but aborted on both occasions. She subsequently conceived 11 months after transplantation while receiving cyclosporin A 400 mg (6·6 mg/kg), prednisolone 7·5 mg, and atenolol 50 mg daily. The cyclosporin was reduced to 300 mg (4·9 mg/kg) at 14 weeks' gestation. She remained normotensive throughout pregnancy and did not have proteinuria. Serum creatinine and urea concentrations did not exceed 108 μmol/l and 9·4 mmol/l respectively. The whole blood cyclosporin A concentration measured at 18 weeks' gestation (by radioimmunoassay) was 959 μg/l (therapeutic range 250-1000 μg/l). White cell and platelet counts were within normal limits.

Serial ultrasonography, measuring fetal head and abdominal circumferences, showed appreciable symmetric growth retardation and a reduction in the volume of liquor. The pregnancy was ended at 30 weeks by caesarean section, and a live male infant weighing 820 g was delivered. The Apgar scores were 9 and 9 at one and five minutes respectively. The infant was normal apart from a small hydrocele, which resolved spontaneously. The haemoglobin concentration was 177 g/l and the white cell count $4·5\times10^9$/l. Serum bilirubin concentration did not exceed 153 μmol/l. There was no evidence of hepatotoxicity or nephrotoxicity.

Comment

Little is known about the safety of cyclosporin during pregnancy. Unpublished data from Sandoz (Drug Monitoring Centre, September 1986) document 24 completed pregnancies in which cyclosporin was used throughout. From these and published data 16 cases can be identified in which gestational age at delivery, birth weight, and the presence of associated antenatal complications (for example, hypertension, diabetes) are known. In 15 cases concomitant treatment was given, most commonly corticosteroids and hypertensive agents.

The table documents these 16 cases. Nine of the 16 infants were growth retarded, with six being severely growth retarded (below the third centile). Intrauterine growth retardation is a well recognised complication of pregnancy in recipients of allografts given conventional immunosuppression, occurring in 8-45%[4]; it seems to occur more commonly in the presence of impaired renal function and hypertension. Of the 16 cases documented, however, five showed growth retardation in the absence of hypertension and renal dysfunction.

Details of pregnancy in women receiving cyclosporin

Case No	Maternal age (years)	Dose of cyclosporin (mg/day)	Gestational age at delivery (weeks)	Birth weight (g)	Centile of birth weight
		Pregnancy complicated by hypertension or diabetes, or both			
1	28	420	28	1060	Between 10th and 50th
2	29	350	32	2000	Above 50th
3	37	Not known	40	3030	Between 3rd and 10th
4	34	360	35	2300	Between 10th and 50th
5	28	400	31	1180	On 3rd
6	19	300	32	1060	Below 3rd
7	38	500	34	1120	Below 3rd
8	Not known	Not known	33	1260	Below 3rd
Mean	30·4	388	33·1	1596	
		Uncomplicated pregnancy			
9	27	450	38	2980	Between 10th and 50th
10	26	460	37	3200	Above 50th
11	24	260	40	2890	Between 3rd and 10th
12	21	150	35	2090	On 10th
13	36	Not known	38	2370	Below 3rd
14	32	550	34	1520	On 3rd
15	31	300	30	820	Below 3rd
16	Not known	Not known	33	1020	Below 3rd
Mean	28·1	362	36	2111	

The possibility of a direct effect of cyclosporin on fetal growth, independent of the condition necessitating its use, should be considered. Placental transfer of the drug, which has a low molecular weight (1203 daltons), is well recognised and seems to be dose related.[3] Considerable growth retardation and fetal death occurred in rats when cyclosporin was administered at 25 mg/kg but not when the dose was reduced to 10 mg/kg.[5]

It would seem prudent, therefore, to maintain plasma cyclosporin concentrations as low as possible; lower doses of cyclosporin are used today than was the case in 1984. Close monitoring of cyclosporin concentrations and transplant function is essential, as is intensive monitoring with serial ultrasonography, measuring the variables that show fetal growth retardation. Further data on cyclosporin treatment in pregnancy are required before any firm conclusions can be drawn, but there is cause for concern.

1 European Multicentre Trial Group. Cyclosporin in cadaveric renal transplantation: one year follow up of a multicentre trial. *Lancet* 1983;i:986-90.
2 Lewis GJ, Lamont CAR, Lee HA, Slapek M. Successful pregnancy in a renal transplant recipient taking cyclosporin A. *Br Med J* 1983;**286**:603.
3 Klintmalm G, Althoff P, Appleby G, Segerbrandt E. Renal function in a new born baby delivered of a renal transplant patient taking cyclosporin. *Transplantation* 1984;**38**:198-9.
4 Lau RJ, Scott JR. Pregnancy following renal transplantation. *Clin Obstet Gynaecol* 1985;**28**:342.
5 Mason RJ, Thomson AW, Whiting PH, *et al*. Cyclosporin induced fetotoxicity in the rat. *Transplantation* 1985;**39**:9-12.

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Clinical carpal scaphoid injuries

The management of clinical carpal scaphoid injury is controversial. Junior and senior medical staff, aware of the sequelae of fractures of the scaphoid, give intensive treatment and are reluctant to discharge patients. Some workers advocate a long arm case for one month[1] while others consider scaphoid injury to be an illusion.[2]

Patients, methods, and results

The records of patients presenting with clinical scaphoid injuries were reviewed retrospectively from January to September 1984 and prospectively from November 1985 to July 1986. The injuries were defined as recent wrist trauma with localised tenderness over the scaphoid bone and normal radiographs. The number of plaster casts required, duration of treatment, symptoms at three weeks, and final diagnosis were recorded. Standard management was to obtain anteroposterior, lateral, and oblique radiographs on presentation, immobilise the joint for three weeks with a short arm cast incorporating the thumb, and then obtain further radiographs. If tenderness persisted radiography was repeated. The radiographs were viewed by all of us.

Of the 164 patients seen, five studied retrospectively were excluded because a fracture was evident in the initial radiographs on review. The remaining patients comprised 80 studied retrospectively and 79 studied prospectively. Their average age was 27 (range 13-70).

Altogether 148 patients presented within 24 hours after injury and 153 within four days. One hundred and eighteen had one plaster applied, 29 had two, six had three, and six had more than three. One hundred and four patients had two radiographs taken, 40 had three, seven had four, and eight had more than four. Twenty two patients were reviewed twice, 67 three times, 22 four times, 39 five times, and nine more than five times. Thirty nine patients still had tenderness at three weeks (table); 30 of these had normal radiographs throughout their treatment. De Quervain's tenosynovitis was diagnosed in two patients.

In nine patients fractures were apparent for the first time at three weeks: three were of Lister's tubercle, one of the distal radius, one of the lunate, and four of the scaphoid. One of these patients (studied retrospectively) was excluded as only views of the wrist had been taken initially. Therefore, three patients (2% of patients presenting with clinical scaphoid injuries) were ultimately proved to have scaphoid fractures. All three fractures were observed only in those patients who still had tenderness at three weeks. No fractures were observed in patients without tenderness at three weeks.

Outcome of treatment of 159 patients for clinical carpal scaphoid injury

	No	Average duration of treatment (days)	
		Time in plaster	Entire treatment
No tenderness at 3 weeks	120	22	32
Tenderness at 3 weeks	39	46	92

Comment

Clinical scaphoid fracture is a definite entity. The 2% incidence we found by radiography at three weeks is low and correlates with the findings of others.[3] These fractures healed without complications but required three months' immobilisation. Patients with tenderness at three weeks and no fractures evident on radiography pose a problem. Serious consideration should be given before the joint is immobilised in plaster in these cases: a delay in treatment does not preclude union even of proved fractures.[4]

Treatment demands clinical and radiographic examination to exclude a fracture or injuries such as scapholunate dissociation. Radiographs may be supplemented with a view in 30° angulation to the elbow.[5] When no fracture is observed the wrist should be immobilised with an easily fitted splint. Patients should be reassessed clinically and radiologically at three weeks, and those with a visible fracture should start conventional treatment. Patients with normal radiographs who still complain of tenderness should be reviewed again, but attendances beyond six weeks should be discouraged. This regimen will reduce the use of plaster casts and outpatient attendances. Reusable splints may be cost effective, though plaster casts are sometimes necessary for soft tissue injuries. Initial tenderness over the scaphoid is not necessarily specific to fractures of the scaphoid; the rate of fractures missed initially (3%) is compatible with the rate missed on examination by junior doctors.

1 Hubbard LF. Fractures of the hand and wrist. In: Evarts CM, ed. *Surgery of the musculo-skeletal system*. Vol 1. New York: Churchill Livingstone, 1983:92.
2 Duncan DJ, Thurston AJ. Clinical fractures of the carpal scaphoid—an illusionary diagnosis. *J Hand Surg [Br]* 1985;**10**:375-6.
3 Leslie IJ, Dickson RA. The fracture carpal scaphoid. *J Bone Joint Surg [Br]* 1981;**63**:225-30.
4 Dunn AW. Fractures and dislocations of the carpus. *Surg Clin North Am* 1972;**52**:1513-38.
5 Stripp WJ, Murray RO, Jacobson HG. *Special techniques in orthopaedic radiology*. Edinburgh: Churchill Livingstone, 1979.

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Body building and myoglobinuria: report of three cases

Myoglobinuria is a syndrome characterised by the passage of dark urine due to massive muscle necrosis. It is related either to disorders of muscle metabolism or to excessive exercise of presumably normal muscle.[1,2] Several cases of exertional rhabdomyolysis have been reported, such as in status epilepticus, prolonged myoclonus, dystonia, military training, marathon running,[1,2] and weight lifting.[3] We report three cases of myoglobinuria that occurred after a first session of body building.

Case reports

Case 1—A 20 year old medical student, a keen skier and tennis player, had never experienced cramps or myalgias after exercise, including a four hour tennis match. After his first one hour session of body building, aimed chiefly at strengthening pectoral and abdominal muscles, he complained of severe muscle pain and weakness and of passing dark urine. Several days later he still had pain and his father, a doctor, suggested routine laboratory tests and measurement of serum creatine kinase activity. The routine tests gave normal results but serum creatine kinase activity was 10 times higher than normal. Four months later he was referred to us. Neurological examination showed an athletic young man with normal strength and reflexes. Serum creatine kinase activity and results of electromyography were normal. The forearm ischaemic exercise test[4] induced a normal increase in venous lactate. An open biopsy sample of quadriceps muscle showed normal morphology and ultrastructure. Staining with periodic acid Schiff, Sudan black B, and oil red O and histochemical staining for lactate dehydrogenase, succinic dehydrogenase, reduced nicotinamide adenine dinucleotide tetrazolium reductase, cytochrome c oxidase, phosphorylase, phosphofructokinase, and adenylate deaminase gave normal results. Biochemical investigations on muscle homogenate (table) showed no enzyme deficiencies.

Case 2—A 23 year old student regularly played competitive football. After his first session of body building in the same club as case 1 he experienced muscle pain and weakness and passed dark urine. One week later the pain persisted and he attended his family doctor (father in case 1). Routine laboratory tests showed nothing abnormal, but serum creatine kinase activity two weeks after the episode of dark urine was five times higher than normal. The patient was admitted one month later and neurological findings, serum creatine kinase activity, and results of electromyography and the forearm ischaemic exercise test were all normal. Morphology, ultrastructure, and results of histochemical and biochemical studies of an open biopsy sample of quadriceps muscle were also normal.

Case 3—A 34 year old doctor was a skier and horse rider. After his first session of body building at a different club from that in cases 1 and 2 he complained of muscle tenderness and weakness and voided dark urine. Three days later the serum creatine kinase activity was 180 times the normal value but routine laboratory tests gave normal results. At 10 days the muscle pains had disappeared and creatine kinase activity had returned to normal. On admission two months later neurological findings, result of the forearm ischaemic exercise test, creatine kinase activity, results of electromyography, and a quadriceps muscle biopsy specimen (table) were all normal.

Biochemical studies of muscle (enzyme activities expressed as nmol/min/mg non-collagen proteins)

Enzyme	Case 1	Case 2	Case 3	Control range (n=10)
Phosphorylase	0·29	0·22	0·17	0·12 -0·30
Phosphoglucomutase	0·080	0·069	0·073	0·020-0·100
Glucosephosphate isomerase	0·97	0·77	0·95	0·37 -1·37
Phosphofructokinase	0·39	0·42	0·30	0·23 -0·47
Aldolase	0·67	0·70	0·62	0·61 -0·71
Glyceraldehyde-3-P-dehydrogenase	1·97	2·03	2·79	0·79 -4·03
Phosphoglycerate kinase	1·56	1·67	1·73	0·33 -3·17
Phosphoglycerate mutase	1·68	1·92	1·73	0·67 -3·03
Enolase	0·42	0·53	0·27	0·10 -1·34
Pyruvate kinase	1·43	1·22	1·57	0·55 -3·31
Lactate dehydrogenase	2·36	2·78	3·91	0·76 -5·60
Carnitine palmitoyltransferase:				
Forward	0·628	0·260	0·170	0·147-0·587
Isotope exchange	0·690	0·340	0·299	0·132-0·772
Reverse	6·930	3·820	2·970	1·260-9·260

Comment

These cases may be classified as myoglobinuria due to excessive exercise. The results of laboratory tests and investigations on muscle biopsy tissue ruled out myoglobinuria due to metabolic defects.[1,2] We cannot exclude unknown enzyme deficiencies as the cause of the myoglobinuria in these patients but the occurrence of a single episode in well trained subjects makes this unlikely. That the episode occurred under the same conditions in all three patients suggests a close relation between exercise and rhabdomyolysis.

Body building has not been mentioned among the different kinds of exercise causing myoglobinuria[1-3] but has been reported in association with increased serum creatine kinase activity in one patient.[5] In contrast with other types of physical activity, body building uses muscles usually less trained, such as the pectorals, trapezii, and abdominal muscles; hence it might cause myoglobinuria in people regularly engaged in sports. The occurrence of myoglobinuria in our patients after their first session of body building aimed at strengthening pectoral and abdominal muscles supports this hypothesis.

Given that our patients (a medical student, student, and doctor respectively) were particularly likely to attach importance to their symptoms we conclude that many other such cases may go unrecognised. We therefore recommend caution for anyone—including healthy sporting subjects—undertaking their first sessions of body building.