140/90 (5.1/2.7) mm Hg). All patients were well six to 77 weeks after transplantation, and none showed appreciable evidence of rejection in a cardiac biopsy specimen. One patient had a mild increase in venous pressure. In all patients the plasma creatinine concentration was less than 162 $\mu\text{mol/l}$ (1.8 mg/100 ml). Immunosuppression was with cyclosporin A and azathioprine. Five patients were receiving antiplatelet treatment with low dose aspirin and dipyridamole and two with aspirin alone. Six patients were also receiving vasodilator treatment with either nifedipine or hydralazine. All subjects were studied taking their normal diets. Blood was collected in the morning after 10 minutes' sitting and atrial natriuretic peptides measured by radioimmunoassay after extraction.³

Plasma atrial natriuretic peptide concentrations (figure) were significantly higher in the cardiac transplant recipients (mean 19.4 (SE 3.9) ng/l) than in the controls (7.3 (1.2) ng/l) ($p < 0.01$, unpaired *t* test and Wilcoxon rank sum test).

Discussion

The mechanisms underlying the raised plasma atrial natriuretic peptide concentrations in the cardiac transplant recipients are not clear. Recent studies have reported raised values in patients with congestive heart failure⁴ and high blood pressure.⁵ The single patient in our series with clinical features of cardiac failure, however, had one of the lowest atrial natriuretic peptide concentrations, and the patients and controls were well matched for blood pressure. In human cardiac transplantation the patient's own heart is removed (apart from the inflow tracts of the systemic and pulmonary veins) together with the posterior wall of the left atrium. The entire donor heart including the great vein inflow sites is transplanted, so that there is around a quarter more atrial tissue in the heart after transplantation is complete. This increased atrial tissue mass may have contributed to the raised plasma atrial natriuretic peptide concentrations in our patients. The transplanted

heart is denervated and remains so for many months after operation²; there is, however, residual innervation of the recipient heart.

From this study alone it is not clear to what extent denervation of the donor atrial tissue may have been responsible for the raised atrial natriuretic peptide concentrations. There was considerable variation among the patients in the concentration of plasma atrial natriuretic peptides, which was not related overtly to cardiac function, arterial pressure, plasma creatinine concentration, or type of drug treatment. These findings seem to suggest that the transplanted atria are secreting atrial peptides. In addition, these results appear to show that in man as well as in other species⁵ innervation is not obligatory for atrial natriuretic peptide secretion to occur. Nevertheless, this cannot be established from our study. To do so will require further studies to determine the relative contribution of donor and recipient atrial tissue to atrial natriuretic peptide secretion.

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Dialysis arthropathy: amyloid or iron?

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Abstract

The clinical, biochemical, radiological, and pathological features in five cases of dialysis arthropathy were analysed. All patients were receiving long term haemodialysis and had had multiple blood transfusions. The arthropathy affected both large and small joints, was predominantly bilateral, and in all cases was associated with the carpal tunnel syndrome. In some instances joint pain was exacerbated during dialysis. In four cases the serum ferritin concentration was raised. Radiological examination showed a few juxta-articular cysts and erosions but most affected joints looked normal. All synovial tissue examined showed amyloid, which stained immunohistochemically for β_2 microglobulin. Large amounts of iron were present in synovial tissue from affected joints.

It is suggested that the deposits of iron, rather than amyloid, in synovial tissue may be the cause of the arthropathy. Iron may be derived locally as a result of haemarthrosis or it may be a manifestation of systemic iron overload.

Introduction

Dialysis arthropathy is a complication of long term haemodialysis.¹⁻³ It is predominantly bilateral, affecting both large and small joints, and is strongly associated with recurrent carpal tunnel syndrome. The cause is unknown but recent reports have emphasised the presence of amyloid in carpal tunnel tissue, bones, and synovium from affected joints.^{4,5} In the case of carpal tunnel tissue this amyloid has been characterised biochemically as β_2 microglobulin,⁶ probably derived from high circulating concentrations. The questions remain, however, whether the finding of amyloid in these joints is incidental and whether there is some other cause for the arthropathy.

Patients, methods, and results

We investigated five patients, who were representative of around 30 patients with dialysis arthropathy being studied. They underwent rheumatological assessment using a detailed form and were the first to have synovial tissue examined histologically. None had evidence of systemic amyloidosis.

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There was no tissue type predominance. All five patients were dialysed twice weekly using cuprophane membranes. Tables I, II, and III give the clinical details of the patients, their rheumatological and radiological characteristics, and the serological and biochemical results, respectively.

HISTOLOGICAL STUDIES

Synovial tissue was obtained at knee arthroscopy (cases 1 and 2), at hip replacement for acetabular fracture (case 4), during an ankle extensor tendon decompression (case 3), and from shoulders, hips, knees, and carpal tunnels at necropsy (case 5) (figure).

Large amounts of amyloid were detected in Congo red stained sections of the four synovial biopsy specimens (cases 1-4) and in all the synovial tissue taken at necropsy from unaffected as well as affected joints in case 5, with small amounts in carpal tunnel tissue. Congo red positivity was preserved after pretreatment with permanganate, consistent with the amyloid not being of type A.⁷ It stained positively for β_2 microglobulin by an immunoperoxidase method.

Additional consistent changes in the four biopsy samples and in tissue from the affected left shoulder in case 5 were (a) mild synovial lining layer hyperplasia with organising fibrinous exudate and (b) very prominent

haemosiderin deposits in stromal macrophages and connective tissue with smaller amounts in lining cells. There was a minimal stromal inflammatory cell infiltrate of lymphocytes and histiocytes. Synovial tissue from the hips in case 5 (unaffected by arthropathy) showed some haemosiderin deposits but no lining layer hyperplasia. Urate crystals were not detectable in tissue fixed in alcohol from cases 1, 2, and 4 and no other crystalline material was seen in any of the samples examined.

Small amounts of amyloid were present in blood vessels from rectal submucosa and brain in case 5. None was detectable in heart, lungs, liver, spleen, and kidney.

Discussion

These five patients were representative of many having long term haemodialysis who develop bilateral pain, stiffness, and limitation of movement, particularly in the arms and hands. Soft tissue swelling and effusions were less common. Associated carpal tunnel syndromes result in disabling weakness and deformity of the hands. Radiological findings were variable and, as described previously, bone cysts, periarticular erosions, and joint narrowing were some-

TABLE I—Details of patients

Case No	Sex and age (years)	Diagnosis	Years of haemodialysis	No of carpal tunnel releases	Joint pain worse during dialysis	Warfarin	Total blood units transfused in past five years	Years from parathyroidectomy
1	M 42	Obstructive uropathy	20	1	No	Nil	Nil*†	11
2	M 45	Glomerulonephritis	15	3	Yes	Yes	36†	8
3	M 40	Obstructive uropathy	20	5	Yes	Nil	59†	Not done
4	F 63	Polycystic kidney disease	7	1	Yes	Yes	4	10 Months
5	F 59	Reflux nephropathy	18	3	Yes	Nil	13†	10

*Siderosis found on liver biopsy five years previously.

†Multiple blood transfusions previously.

TABLE II—Rheumatological characteristics and findings of radiological skeletal survey

	Hands			Wrists	Elbows	Shoulders	Cervical spine	Lumbar spine	Hips	Knees	Ankles	Feet
	Distal inter-phalangeal	Proximal inter-phalangeal	Metacarpophalangeal									
Case 1	Right	†	ER(3)	† C trapezoid		† Labrum glenoidale calcification	†	† Scoliosis		† ef		ER(1) metatarsophalangeal
	Left	†	ER(5)	† C ulna		†				† ef		
Case 2	Right	†	† f	†		† S humeral head	†	†	† Osteophyte, osteonecrosis	† ef	†	
	Left	†	† f	† ER scaphoid		†			†	†	† ef	
Case 3	Right	†	† f	†	†	† S humeral head	†	†	Osteonecrosis	† ef N	†	†
	Left	†	† f	†		† C humeral head			†	† ef N	†	† S, N(1)
Case 4	Right	† ER(3)	† ER(2)	† Subluxation carpometacarpal (1)			†	†	†	N		
	Left	†	ER(2, 4)	†					† C greater trochanter	N		
Case 5	Right			†	†	† Inferior subluxation, C humeral head			† C femoral head			
	Left	† f	† f	†	†	† Lesser tuberosity irregularity		†				

Rheumatological findings—†=Clinical joint involvement, principal symptoms and signs being pain, stiffness, and limitation of movement. ef=Effusion. f=Poor fist closure.

Radiological findings—ER=Erosion. C=Cyst(s). N=Joint space narrowing. S=Sclerosis. Figures in parentheses are digit numbers.

TABLE III—Serological and biochemical results

Case No	Rheumatoid factor			Parathyroid hormone (normal <0.5 µg/l)	Aluminium (normal <3.7 µmol/l)	Ferritin (normal 20-200 µg/l)	Alkaline phosphatase (normal 90-310 iU/l)	Calcium/phosphate product (normal <5.2 mmol/l)	Urate (normal 100-400 µmol/l)
	Latex test	Rheumatoid arthritis haemagglutination titre (normal <1/160)	Antinuclear factor						
1	Weakly positive	Not done	Weakly positive, homogenous	<0.10	1.60	268	93	4.6	391
2	Negative	<1/40	Negative	0.29	0.42	2260	150	3.1	410
3	Weakly positive	Not done	Negative	<0.10	0.55	7800	510 (liver)	5.1	493
4	Negative	<1/40	Weakly positive, homogenous	0.28	1.76	31	220	4.4	387
5	Negative	<1/40	Negative	0.41	2.01	323	230	3.4	490

Conversion: SI to traditional units—Aluminium: 1 µmol/l≈2.7 µg/100 ml. Calcium/phosphate product: 1 mmol/l≈14 mg/100 ml. Urate: 1 mmol/l≈17 mg/100 ml.

times present (table II).^{5,8,9} There was little correlation between physical signs and radiological abnormality.

The cause of the dialysis arthropathy remained obscure, with no consistent biochemical findings¹ and no crystals detected either in synovial fluid or in synovial biopsy samples. The weakly positive rheumatoid and antinuclear factor test results (table III) were thought not to be relevant.

All synovial tissue examined showed large amyloid deposits. Preliminary immunoperoxidase results showing staining of amyloid with antibody to β_2 microglobulin agreed with a recent study which used immunofluorescence.¹⁰ Patients being treated by haemodialysis have very high concentrations of β_2 microglobulin owing to

its impaired excretion and metabolism by the kidney in end stage renal failure. There is minimal clearance across cuprophane and opposed to polyacrylonitrile membranes.^{11,12}

It has generally been assumed that synovial amyloid deposits are responsible for dialysis arthropathy.⁵ The fact that they were equally prominent in unaffected joints as in affected joints in case 5, however, suggests that their presence may be incidental. The role of amyloid in the pathogenesis of a rather similar arthropathy which sometimes occurs in multiple myeloma has been questioned recently,¹³ and amyloid deposits in synovium and in articular cartilage are very common with aging.¹⁴

Our results show that there is both clinical and pathological evidence that haemarthrosis and possibly iron overload may be important aetiological factors in dialysis arthropathy. Two anephric patients (cases 2 and 3) had grossly raised ferritin concentrations (table III) associated with multiple transfusions. Four of the five patients had occasional exacerbations of their joint pain during dialysis, and in case 3 blood was aspirated from the patient's shoulder after one such occasion. Haemarthrosis may be precipitated by heparinisation necessary for haemodialysis, and impaired platelet function may be contributory. In addition, two of the patients were taking warfarin.

The histological changes present in synovium from affected joints (apart from amyloid deposits) closely resembled those seen in an animal model of recurrent haemarthrosis¹⁵ and were also similar to those described in haemophilia.¹⁶ There were some similarities to the synovial biopsy findings in haemochromatosis arthropathy,¹⁷ which may have been an aetiological factor in the three patients with a raised serum ferritin concentration and a history of numerous blood transfusions. Whether the synovial hemosiderin deposits in our patients were the result of haemarthrosis or iron overload remains unknown, though both may have been contributory. Whatever their origin iron deposits may cause arthropathy in a manner similar to that proposed for rheumatoid arthritis,¹⁸ by production of free radicals with resultant peroxidation and synovitis.

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Histological sections of representative synovial tissue (case 3). (a) Haematoxylin and eosin stained, showing synovial hyperplasia and black deposits, which in (b) stained positively by Perl's method for iron. (c) Congo red. Amyloid deposits stained positively (grey areas, left) and showed birefringence when examined through crossed Polaroids (right). Birefringent areas which did not stain positively were collagen fibres.