Leaders

Amyloid, advanced glycation end products, and dialysis related arthropathy

Dialysis associated arthropathy (DRA) is a syndrome peculiar to long term dialysis patients. It includes large and small joint symptoms, pathological fractures through bony cysts and an axial spondyloarthropathy, and is closely associated with carpal tunnel syndrome. It is characterised by deposition of β2 microglobulin (β2M) as an amyloid protein. This was first linked to the osteoarticular syndrome 12 years ago.1 Several other forms of bone and joint pathology also occur more frequently in dialysis patients, including secondary hyperparathyroidism, osteoporosis, gout, pseudogout, and aluminium induced bone disease.2

Prevalence of DRA is closely related to age and years of dialysis treatment. Symptoms develop in some patients within four to five years of treatment and are almost universally present in those who have been treated by haemodialysis for 15 years.2–4 The number of patients in this at risk group is steadily increasing; in Australia the proportion of patients with over 10 years exposure to dialysis treatment has remained constant around 6% over the past decade but the total number of patients needing dialysis treatment has doubled and the proportion over 65 years rose from 18% to 35%.5 Other Western countries face a similar problem.

Several active areas of investigation and debate remain. The nature of the β2M deposition has been intensively studied, with recent demonstration of non-enzymatic modification of β2M to form advanced glycation end products (AGEs). The roles of different dialysis membranes and techniques in the production and clearance of β2M and the genesis of DRA continues to be actively investigated, although there have been few major technological advances in this area over the past five years.

Physiology

β2M is a 11.8 kDa polypeptide. The light chain of the HLA class I complex, it is expressed on the cell membrane of all nucleated cells. Freely filtered across the glomerulus, it is then reabsorbed and metabolised by the proximal tubular cells. In chronic renal failure levels are increased in inverse relation to the glomerular filtration rate, and in dialysis patients can reach up to 20 times the normal range.2

In addition to impaired clearance, haemodialysis is associated with cytokine release and increased production of β2M.1 Systemic monocyte activation has also been shown with peritoneal dialysis.5

Pathology

The fibrils formed from β2M deposit preferentially in osteoarticular tissue, especially in the carpal tunnel, shoulder, hip, knee, and axial skeleton. Unlike other secondary forms of amyloid, it is deposited intact, without proteolysis or other processing,7 and can be easily visualised with appropriate immunohistochemistry (fig 1).

The amyloid protein deposits in DRA consist of fibrils complexed with amyloid P component, a glycoprotein identical with serum amyloid P component. Concentrations of serum amyloid P component are increased in patients with chronic renal failure and dialysis, but whether they contribute to increased amyloid deposition is unclear.8–10

A major recent development has been the finding that the β2M amyloid fibrils are modified (by non-enzymatic combination of protein amino groups with sugar aldehyde groups) to form AGEs.11 The AGEs are acidic isoforms and are more likely to form fibrils.6 It is unclear whether AGEs are generated in the circulation or in situ, but generation is likely to be enhanced by the oxidative stress associated with chronic uraemia.11 The existence of a receptor for AGE on monocytes and macrophages, and release of TNFα and IL1β stimulated by purified AGE modified β2M has been shown leading to the proposal of AGEs as the mediators of β2M related bone disease.12

Clinical presentation

In a detailed clinical survey at our institution of patients with more than 10 years dialysis treatment, 80% had pain or stiffness in large joints, 64% restriction of movement, 93% pain or stiffness in hands, 43% pain or stiffness in axial joints, and 43% clinical evidence of carpal tunnel syndrome.2 These results are consistent with other reports.3–10 14 All have shown that the prevalence of symptoms and radiographic changes is related to age and years of dialysis treatment. Postmortem data confirm the influence of age and dialysis duration, but suggest earlier and more prevalent β2M amyloid deposition than clinically apparent; Jadoul et al recently showed a prevalence of joint β2M of 21% after two years and 90% after seven years of dialysis treatment.15

The joint most commonly afflicted by DRA is the shoulder, causing either pain and stiffness (particularly at night) or a rotator cuff impingement syndrome. Symptoms in the
fistula arm are often worsened by immobility during dialysis. Joint damage tends to be slowly progressive with occasional inflammatory exacerbations, particularly in metacarpophalangeal joints, which may mimic an acute inflammatory arthritis. Trigger finger, flexor tendon contracture, haemarthrosis, and spontaneous tendon rupture may also occur. Effusions are common in the larger joints; 14 of 26 long term dialysis patients in our hospital had glenohumeral joint effusions seen on magnetic resonance images (MRI). A common accompaniment of β2 amyloid accumulation is carpal tunnel syndrome. Although relieved by surgery, recurrence is common, as is bilateral disease. The combination of carpal tunnel syndrome with DRA in the hand has been shown to lead to a steady decline in hand function in long term dialysis patients.

β2 amyloid deposition within an erosive spondyloarthropathy is well described, especially in the cervical and lumbar spine. Occurrence is well correlated with carpal tunnel syndrome and DRA, and similarly increases in incidence with age and years of dialysis treatment.

Bony cysts containing β2 amyloid can present in several other sites. They are usually asymptomatic, but can become large enough to cause pathological fractures. The carpal bones are the most common site, followed by femur, phalanges and distal radius. Visceral involvement is unusual and tends to occur late. Sites described include the blood vessels, tongue, cutaneous “amyloidomas”, and colonic mucosa.

DRA also occurs in patients dialysed with peritoneal dialysis; in one survey of 56 patients using this treatment modality for more than three years during dialysis treatment, 16 had chronic shoulder pain, eight subchondral bone cysts, and 13 destructive arthropathies.

Diagnostic tests
The symptoms of DRA are far from unique, and a variety of tests have been used to diagnose the relative contribution of β2M amyloid compared with osteoarthritis and various forms of metabolic bone disease. Plain radiology, synovial fluid aspiration, nuclear scans, ultrasound, and MRI have all been described as investigative tools of variable utility. The changes seen by plain radiology are well described; principal features are subchondral bone cysts, especially in the acetabulum, carpal bones, and distal radius and ulna. Although the full pattern is distinctive, it may be impossible to distinguish early changes from osteoarthritis, hyperparathyroidism or even aluminium related bone disease.

Increased serum concentrations of β2M alone do not differentiate patients with β2M amyloid deposition. Several groups have used 131I labelled β2M to study early deposition of β2 amyloid. I labelled serum amyloid P component (SAP) has also been used. Although all have shown deposition in both symptomatic and asymptomatic areas of β2M amyloid, these techniques have suffered from several limitations: supply of the microglobulin or SAP, the high radiation exposure incurred, and poor definition in images in the shoulder and hip area because of high background uptake. They have shown early (presymptomatic) deposition of β2 amyloid and a high prevalence of asymptomatic deposition in long term dialysis patients, but are not routinely available for diagnostic use.

Ultrasound and MRI have particular use in the shoulder, where they both provide accurate imaging of the rotator cuff. Either can distinguish amyloid infiltration from calcific rotator cuff disease; with ultrasound thickened tendons with altered echo texture are seen, and with MRI an intermediate signal is seen in the tendons on T1 sequence and variable signal on T2 sequence. The MRI appearance is characteristic and unlike any other shoulder pathology. Adjacent bony structures are rendered in fine detail (fig 2). We examined with MRI a group of 23 long term dialysis patients and found bony abnormalities in all. Ultrasound is a simpler and cheaper modality, but MRI provides superior definition and may prove a valuable tool to diagnose the presence of β2M deposits, whereas ultrasound will provide functional information about rotator cuff impingement.

Treatment
The optimal treatment for DRA is renal transplantation. It is the only treatment that will reduce β2M concentration to normal. Sustained symptomatic improvement occurs immediately after transplant but the timing of the

Figure 1  Skeletal muscle removed at surgery of shoulder damaged by β2 amyloid, with β2M amyloid deposits demonstrated by immunoperoxidase (arrow).

Figure 2  T2 weighted coronal section from MRI shoulder with features of dialysis arthropathy. The supraspinatus tendon is greatly thickened, and a large bony cyst can be seen in the humeral head (at surgery the specimen in figure 1 was obtained).
improvement suggests the cause of the improved symptoms may be immunosuppression (in particular corticosteroids), with only minor resolution of established deposits. Unfortunately for most patients transplantation is not an option. In Australia only 34% of dialysis patients are awaiting transplantation, and even in those less than 65 years old a substantial number (41%) are not on active transplant lists for various reasons. β2M clearance during dialysis can be improved using different dialysis membranes and techniques. Dialysers are characterised in terms of their “biocompatibility” (stimulus to β2M production) and “flux”, which refers to the pore size and therefore rate of β2M clearance. Newer high flux biocompatible dialysers use either synthetic or substituted cellulose membranes (in contrast with the older cellulose membranes), and have been shown to reduce circulating β2M concentrations. Whether this increased clearance translates to a lower incidence of DRA is not clear. Retrospective studies have produced conflicting results. The EDTA Registry study showed no significant difference in incidence of DRA in a case control survey, but a larger study by van Ypersele de Strihou et al. showed a significant decrease in the rate of radiological DRA, but not carpal tunnel syndrome with the highly permeable polyacrylonitrile (AN69) membrane. Available prospective data support a reduction in the incidence of DRA, although it is not clear whether occurrence is delayed or prevented. Further prospective data recently published suggest the prevalence of DRA in the dialysis population is falling, but investigators were unable to relate this to changed patterns of membrane use. Despite these findings, there is considerable variation of opinion and practice between countries in the use of high flux membranes, with much higher rates in Europe compared with the United States. A major randomised study (the NIH HEMO trial) currently in progress in the United States will clarify the impact of these changes.

The other technique that improves β2M clearance is haemodiafiltration. This refers to the addition of an ultrapure solution to blood, and the filtration of an equivalent volume across a (high flux) membrane in addition to ultrapure solution to blood, and the filtration of an equivalent volume across a (high flux) membrane in addition to.

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S P MCDONALD, P T H COATES and A P S DISNEY

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