Long term effect of renal transplantation on dialysis-related amyloid deposits and symptomatology

S I-YEN TAN, ASHLEY IRISH, CHRISTOPHER G. WINEARLS, EDWINA A. BROWN, PETER E. GOWER, ELAINE J. CLUTTERBUCK, SHERIL MADHOO, J. PETER LAVENDER, MARK B. PEPSY, and PHILIP N. HAWKINS

Immunological Medicine and Renal Units, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London; Renal Unit, Churchill Hospital, Oxford, and Renal Unit, Charing Cross Hospital, London, England, United Kingdom

Long term effect of renal transplantation on dialysis-related amyloid deposits and symptomatology. We report the five year outcome of nine patients with dialysis-related amyloid (DRA) who underwent successful renal transplantation (RT) and six patients who remained on hemodialysis (HD). Amyloid bone cysts, a radiologic feature of DRA, and scintigraphy with 123I-labeled serum amyloid P component (SAP), a specific technique for evaluating amyloid deposits in vivo, were monitored and compared with clinical features. In all HD patients there was clinical, scintigraphic and/or radiologic evidence that DRA progressed. In contrast, eight of the RT patients experienced profound early relief of DRA symptoms following transplantation that persisted throughout follow-up, despite the reduction or withdrawal of corticosteroids. Amyloid bone cysts improved in four patients and SAP scans demonstrated regression of articular amyloid in eight out of nine cases. The modest radiographic improvement suggests that amyloid is mobilized more slowly in bone cysts than elsewhere or that cystic bone is remodeled poorly. This is the first objective evidence that DRA regresses following renal transplantation, and suggests that this may contribute to the long-term relief of DRA symptoms in transplant recipients who discontinue corticosteroids.

Dialysis-related amyloid (DRA) is a painful condition that is common in long-term hemodialysis (HD) populations [1–3]. A characteristic arthropathy and carpal tunnel syndrome (CTS) are associated with amyloid deposition in and around the joints, and systemic DRA may occur as a late event [4]. The amyloid fibrils are composed of β2-microglobulin (β2m) [5], a trace protein that is normally catabolized in the kidney. β2m is retained in renal failure and during dialysis, and high plasma levels of the protein are essential for the development of DRA [3, 6].

In the absence of any specific treatment, an important objective in DRA is to reduce the plasma concentration of β2m to normal, which presently can be achieved only through renal transplantation [2, 3]. If performed early, DRA can be prevented but even after many years this approach relieves arthralgic symptoms rapidly, and halts radiologic progression of DRA bone cysts [7].

Scintigraphy and turnover studies with radioiodinated serum amyloid P component (SAP) are effective methods for monitoring amyloid deposits of AA, AL and variant transthyretin types [8–14]. Labeled SAP accumulates specifically in amyloid, enabling deposits to be evaluated directly and quantitatively in vivo. DRA deposits have also been imaged with 123I-SAP although certain sites were favored, especially the wrists and knees, by being distant from the intense central blood-pool background signal [15]. Turnover studies with 123I-SAP indicated that the total amount of amyloid in patients with HD was small.

We now report a prospective five year study of patients with symptomatic DRA who underwent renal transplantation. Outcome was evaluated with respect to clinical status, radiology and SAP scintigraphy and was compared with a control group of patients who remained on HD.

Methods

Patients

Fifteen patients with clinical and histological evidence of DRA (aged 41 to 66 years, 10 males, 5 females) who had undergone hemodialysis for a median of 18 years (interquartile range, 14 to 21 years) were studied prospectively for five years. At completion, six patients were still receiving dialysis (HD group) whereas nine had successfully undergone renal transplantation (RT group). Three RT patients had been transplanted shortly before recruitment. The median duration post transplantation was 4.5 years (range, 2 to 7.5 years). The HD and RT groups were similar with respect to follow-up period, age, sex and total duration of dialysis.

Assessment

Symptoms. Clinical features of dialysis arthropathy were evaluated by a rheumatologist. At baseline each affected hip, knee, shoulder and wrist, including carpal tunnel syndrome (CTS), scored one point (maximum 8 points). At completion, each joint scored 2 if worse (maximum 16 points), one if unchanged, 0.5 if improved, or zero if features had resolved. An additional point was given for any joint affected at follow-up which had been normal at baseline. The relationship between symptoms, renal transplantation and corticosteroid dosage was recorded.

Radiology. X-rays of the hands, wrists, knees, shoulders and hips were obtained at approximately yearly intervals. Previous films were available in each case. The baseline radiologic joint score comprised one point for each amyloid bone cyst identified using

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282
Fig. 1. Joint scores for symptoms, X-rays and SAP scintigraphy for individual patients in hemodialysis (N = 6) and renal transplant (N = 9) groups at entry and end of study.
rigorous criteria [1]. At completion, cysts that were larger scored 2, one if unchanged and 0.5 if smaller. No cyst resolved completely and new cysts scored an additional point. Radiographs were evaluated “blind” by an experienced skeletal radiologist. In two cases some X-rays were missing.

\textbf{123I-labeled SAP scans and metabolic studies.} Isolation and radiolabeling of human SAP with \textsuperscript{123}I and \textsuperscript{125}I, scintigraphy, and turnover studies were performed as described [8, 9, 16], although the latter were necessarily limited to plasma clearance measurements in anuric patients. Scintigraphs were assessed anonymously by two physicians with experience of 1000 such studies. Serial scans were unavailable for the wrists in one patient and knees in another. Baseline images of the shoulders, wrists, knees and hips were scored one point for each joint in which there was abnormal uptake of tracer (maximum 8 points). At completion each joint scored 2 points if uptake was greater (maximum 16 points), one if unchanged, 0.5 if improved, or zero if the images fell within normal limits; an additional point was given for any joint that became abnormal during the study.

\textbf{Histology.} Biopsies obtained during the study were subjected to routine histologic examination, staining with Congo red [17] and immunohistochemistry with a panel of antisera against amyloid fibril proteins [18].

\textbf{Serum concentration of \(\beta_2m\), SAP and creatinine.} \(\beta_2m\) and creatinine levels were measured in venous blood using standard autoanalyzer techniques. SAP concentration was determined by electroimmunoassay [19].

\textbf{Statistical analysis}

Demographic differences between the patient groups and results of metabolic measurements were sought using the Mann-Whitney U-test. Scores for symptoms, scans and X-rays were analyzed using the Wilcoxon rank tests for paired samples and unpaired groups. \(P < 0.05\) was deemed significant.

\textbf{Results}

\textbf{Symptoms}

At baseline all patients had symptoms of DRA, with the same median of four affected joints in each group. Surgery for CTS had been performed a median of once per patient in each group.

Four of the six HD patients experienced worsening arthralgia, and recurrence or development of CTS (Fig. 1A), two of them requiring surgery. The two patients without progressive symptoms had the shortest follow up.

In the RT group, eight of nine patients reported rapid and substantial relief of arthralgia following transplantation (\(P = 0.01\) for scores at entry and end of study; Fig. 1B). This was sustained despite reduction (\(N = 5\)) or complete withdrawal (\(N = 4\)) of corticosteroids, although symptoms recurred transiently in two cases while tapering. No RT patient required surgery for CTS. DRA symptoms remained after transplantation in one case.

The difference between symptom scores for the HD and RT groups at completion was significant, \(P = 0.018\). The difference between the changes in scores from entry to end of study in the two groups was also significant (\(P = 0.018\)).

\textbf{Radiology}

Amyloid bone cysts were most common in the wrists followed by the hips, shoulders and knees (Table 1). Among patients with baseline radiologic abnormalities, the median number of affected joints per patient was 3.5 in the HD group and 3 in the RT group, while the median number of cysts per affected joint were 2 and 1, respectively.

Among the HD patients, 18 DRA bone cysts in four cases were identified at baseline. At follow-up (Table 1 and Fig. 1C) the cysts were larger and there were \(7\) new cysts, a significant deterioration (\(P = 0.018\)). In contrast, among the \(5\) RT patients with baseline radiographic abnormalities, cyst size decreased and there was ossification in the cyst walls (Fig. 2) in \(4\) affected joints in four patients. None of the 24 cysts resolved (Table 1 and Fig. ID), but there was a significant difference between the HD and RT scores at completion (\(P = 0.02\)). Changes in score during the study were also significantly different between the groups (\(P = 0.018\)).

\textbf{123I-labeled SAP scintigraphy}

Positive scans of at least the wrists were obtained at baseline in all subjects except one HD patient (Fig. 1E). Amyloid was identified frequently in the knees and, less often, the shoulders. Images of hips were non-diagnostic because of their deep location and proximity to the strong masking signal from tracer in the central blood pool. Amyloid was not identified in any other site.

DRA was progressive in five of six HD patients (Fig. 1E): 5 additional joints gave positive images and there was increased tracer uptake in 7 joints that were positive at baseline (Fig. 3). Follow-up studies were unchanged in one HD and one RT patient. In each of the eight other RT patients, amyloid deposits regressed in at least one site (Fig. IF) with tracer uptake reduced in 16 of the 41 joints identified as abnormal at baseline (\(P = 0.01\)). Amyloid decreased below limits of detection in 6 joints in three patients, including all 3 affected joints in one case. Changes in joint score at baseline and completion were significantly different between the two groups (\(P = 0.018\)).

\textbf{Histology}

During the study tissue was resected at carpal tunnel release in two HD patients, and at spinal surgery in two RT patients, one with a fractured cervical vertebra, the other during a decompressive procedure. All tissues contained amyloid that stained specifically for \(\beta_2m\).

\textbf{Serum concentration of \(\beta_2m\), SAP and creatinine}

Among RT recipients serum levels of \(\beta_2m\) and creatinine were significantly lower at completion (median values 3.2 mg/liter and 117 \(\mu\)mol/liter, respectively) than at baseline (45.5 mg/liter and 954 \(\mu\)mol/liter; \(P < 0.001\)), corresponding with restored renal function. The concentration of SAP, which is raised in renal

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{} & \textbf{Renal transplant patients} & \textbf{Hemodialysis patients} & \textbf{}\hline
\textbf{Entry} & \textbf{Completion} & \textbf{Entry} & \textbf{Completion} & \textbf{}\hline
Wrists & 18 & 18 & 14 & 14 & \textbf{}\hline
Shoulders & 0 & 0 & 2 & 3 & \textbf{}\hline
Hips & 5 & 5 & 2 & 8 & \textbf{}\hline
Knees & 1 & 1 & 0 & 0 & \textbf{}\hline
\textbf{Total} & 24 & 24 & 18 & 25 & \textbf{}\hline
\end{tabular}
\caption{Number of amyloid bone cysts}
\end{table}
failure [20], also fell following RT, but not significantly. No changes in serum levels of $\beta_2$m, SAP or creatinine occurred in HD patients.

Metabolic studies

Plasma clearance of $^{123}$I-SAP, which reflects whole body amyloid load, was obtained in four HD and eight RT patients. The plasma concentration of $^{123}$I-SAP after six hours, expressed as the mean (SD) percentage of the injected dose, was 75% (8) at baseline in the HD group and 69% (1) at completion, compared with 75% (4.5) and 76% (7), respectively in the RT group. These trends were not statistically significant. Whole body retention of radioactivity fell within the normal range [9] in all RT patients at completion.

Correlation between clinical features, radiology, scintigraphy and histology

The most frequent presenting feature of DRA was CTS followed by shoulder arthralgia. Scintigraphy and X-rays were positive most often in the wrists. Positive scintigraphy of at least one joint was seen initially in 14 of 15 patients whereas radiologic bone cysts occurred in only nine cases.

At completion, among 31 joints affected clinically in HD patients, DRA was evident radiologically in 11 (35%), and scintigraphically in 17 (55%). Characteristic symptoms were the sole clinical feature of DRA in 8 (26%) of the joints. Conversely, among 32 joints with radiological and/or scintigraphic evidence of amyloid, 9 (28%) were asymptomatic; 2 out of 8 joints with sub-clinical DRA at baseline subsequently became symptomatic.

All but one RT patients experienced profound reduction of
DRA symptoms, while one or both imaging modalities provided evidence of amyloid regression in every case. Amyloid could not be detected in scans of 8 of 41 (20%) joints that had previously been abnormal, although this does not necessarily indicate complete resolution. Scans showed improvement in a further 16 of 41 (39%) joints. Radiology also showed some improvement, but to lesser extent and among fewer joints (4 of 13, 31%). Overall, radiology and scintigraphy improved much less than clinical symptoms.

Baseline wrist radiology and scintigraphy had been positive in

Fig. 3. Serial $^{131}$-SAP scans showing progression of DRA in the hands of a 67-year-old lady who developed symptomatic DRA in both wrists after six years on HD. Images obtained in 1991 (A) show abnormal uptake of tracer into amyloid deposits in the wrists and some small joints of the hands; the uptake was greater in 1994 (B).
both HD patients who developed CTS requiring surgery, but spinal imaging of the two RT patients who underwent surgery was normal.

**Discussion**

The relationship between $\beta_2m$ amyloidosis and dialysis arthropathy remains unclear [21]. Amyloid can be found in most symptomatic sites but silent deposits are frequent [22] and may simply precede symptoms. Other factors influence disease expression and, for example, arthralgia in DRA may respond to corticosteroids [23]. Symptoms often remit dramatically after renal transplantation [3, 7], possibly due to steroid anti-rejection therapy [24, 25] or simply stopping dialysis itself. DRA symptoms improved characteristically after renal transplantation in our patients but,
significantly, did not recur following withdrawal of corticosteroids, indicating that other factors are responsible for remission later on.

The fate of $\beta_2$m amyloid after renal transplantation has been difficult to follow; biopsies are invasive, open to sampling error and can provide only a limited overview. SAP scintigraphy is an alternative method for demonstrating amyloid in vivo based on the specific reversible binding of SAP to all amyloid deposits which occurs in proportion to their quantity [8, 9, 26–29]. Scintigraphic localization of labeled SAP to amyloid is a specific dilution phenomenon in which the tracer equilibrates freely with SAP in the plasma and the larger amount that is concentrated within amyloid deposits. SAP does not accumulate in tissues that do not contain amyloid. This unique dynamic behavior validates prospective labeled SAP studies for quantitative monitoring during all phases of amyloid deposition, steady state and mobilization.

Our results confirm that SAP scintigraphy is moderately sensitive for detecting symptomatic and silent DRA deposits, but joints lying close to the central blood pool background signal yielded consistently poor results. Despite this, it is clear that the extent of articular amyloid is underestimated clinically and radiologically, supporting histological evidence that DRA involvement of joints is often sub-clinical [22]. Our most significant finding, however, was regression of articular amyloid in one or more sites in eight out of nine patients following renal transplantation. This contrasted sharply with progressive amyloid deposition in all but one patient in the HD group.

Radiologic findings accorded with the scans, showing reduction in size of some amyloid bone cysts and ossification at their edges in four out of five patients in the RT group. No cyst progressed in a transplanted patient, whereas the converse was true among all those remaining on HD. The only other prospective radiologic study in DRA [7] showed that progression of cysts did not occur following renal transplantation, but there was no improvement. Our patients were follow-up longer (mean 5.7 years vs. 3.9 years) and may have had less advanced disease and less corticosteroids; there may also have been differences in age, sex, and menopausal status. No cyst in our study regressed substantially, suggesting that amyloid mobilizes more slowly from bone cysts than joints, or that cysts heal poorly even when amyloid within them diminishes.

In labeled SAP turnover studies, the overall proportion of tracer that localized to amyloid was less than 5% of the injected dose, indicating that the whole-body quantity of amyloid in DRA is small compared with systemic AA and AL amyloidosis [9], consistent with autopsy findings. Plasma clearance rates of tracer fell during the study in all HD patients and increased in the RT cases, suggesting net accumulation of amyloid with HD and regression after transplantation, but the changes did not reach statistical significance. Measurements of SAP turnover alone, therefore, were not sensitive enough to monitor changes in the relatively small DRA deposits.

Our results add to the growing body of evidence in AA [11], AL [10, 13, 14] and hereditary transthyretin amyloidosis [12] that amyloid is a dynamic process which frequently regresses when supply of the respective amyloid fibril precursor protein is reduced [30].

Although histological detection of $\beta_2$m amyloid [25] and failure of bone cysts to improve many years after renal transplantation [7] have been interpreted as evidence that DRA cannot regress, such observations may equally well reflect the difficulties in monitoring DRA quantitatively. Regression of amyloid is slow and microscopic residual deposits should be expected for many years after successful intervention. Although scans of some joints that had been abnormal at baseline fell within normal limits after transplantation, this cannot exclude the possibility that residual amyloid might have been evident histologically. Histology and SAP scintigraphy are different but complementary techniques which both demonstrate amyloid specifically [27]. Scans survey the whole body non-invasively and macroscopically, whereas histology is much more sensitive but cannot quantify the whole body amyloid load or reliably monitor progress or regression of deposits generally. Labeled SAP scans have now been performed in over 800 patients worldwide, both in collaboration with us and independently [31]. We anticipate that they will soon become more accessible following successful labeling of SAP with $^{99m}$Tc [32].

In conclusion, we have shown that SAP scintigraphy can be used to monitor articular DRA deposits. Although correlation between symptoms, bone cysts and articular amyloid on scanning was limited, DRA was progressive in all HD patients and regressed in all RT cases. Monitoring bone cysts appears to be a poor surrogate for evaluating the DRA deposits within joints themselves. Finally, our findings suggest that regression of amyloid contributes to the long-term relief of DRA symptoms in renal transplant patients who are able to discontinue corticosteroids.

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Reprint requests to Dr. P.N. Hawkins, Immunological Medicine Unit, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, England, United Kingdom.

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