Characteristics of dialysis-related amyloidosis in patients on haemodialysis therapy for more than 30 years

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Abstract

Background. Dialysis-related amyloidosis is one of the chronic complications of haemodialysis. We conducted an investigation of dialysis-associated amyloidosis in extremely long-term survivors.

Methods. Twenty-one patients on haemodialysis for more than 30 years (‘30+’ group) and 13 patients on haemodialysis for 20–30 years (‘20–30’ group) at Sangenjaya Hospital were enrolled in this study. The frequencies of operations for conditions related to haemodialysis-related amyloidosis were examined.

Results. The mean age at the start of haemodialysis was younger in the ‘30+’ group (29.1 ± 7.3 years) than in the ‘20–30’ group (40.5 ± 8.2 years, P = 0.0003). Eighteen (85.7%) patients had undergone surgery for CTS, six (28.6%) had undergone surgery for trigger finger and six (28.6%) had undergone surgery for cervical destructive spondylarthropathy (DSA) at 30 years after the start of haemodialysis therapy. Patients who were over the age of 30 years at the start of dialysis therapy more frequently underwent CTS operations (100%) than those who were under 30 years of age at the start of dialysis (76.9%; P = 0.025) in the ‘30+’ group at 30 years after the start of haemodialysis. The frequencies of operations for CTS did not differ significantly between the ‘20–30’ group and the ‘30+’ group.

Conclusions. Haemodialysis-associated amyloidosis was common in extremely long-term survivors. Even though the mean age at the start of haemodialysis was younger in the ‘30+’ group than in the ‘20–30’ group, the frequency of operations for CTS did not differ. This may be attributable to the recent advances in haemodialysis technologies.

Keywords: amyloidosis; carpal tunnel syndrome; destructive spondylarthropathy; high-flux membrane; long-term haemodialysis

Introduction

Since its experimental introduction in 1960, haemodialysis has become a widely performed and relatively safe procedure. Therapeutic strategies have been developed, and the number of extremely long-term survivors of haemodialysis therapy has been increasing. Because there are not enough renal transplantation donors in Japan, the duration of haemodialysis therapy is much longer than in other countries [1], and regional differences in the mortality rates of haemodialysis patients have been found highest in the United States and lowest in Japan [1,2]. Therefore, Japan provides an ideal setting for describing patients receiving extremely long-term dialysis. We have previously reported various indexes affecting mortality in patients who have received haemodialysis for more than 30 years [3]. Dialysis-related amyloidosis is one chronic complication of long-term haemodialysis that affects quality of life. Almost no previous reports have discussed amyloidosis in patients receiving maintenance haemodialysis for more than 30 years. In 1985, β₂-microglobulin (β₂-m), with a molecular weight of 11,800 Da, was identified as the major constituent protein of this amyloid [4]. Since then, haemodialysis technology for dialysis-related amyloidosis has been developed. In the present study, we investigated dialysis-associated amyloidosis in patients receiving maintenance haemodialysis for more than 30 years.

Subjects and methods

Twenty-one patients who had been receiving haemodialysis for >30 years (‘30+’ group) at Sangenjaya Hospital as of 1 July 2008 were enrolled in this study. Reverse osmosis treatment for dialysis water was initiated at our hospital in 1988, and the use of high-flux membranes was started at the same time. To compare histological differences, 13 patients receiving haemodialysis for 20–30 years (‘20–30’ group) were also studied.

Background data (age, gender, cause of renal failure) and the medical histories of operations performed
for haemodialysis-associated amyloidosis [such as carpal tunnel syndrome (CTS), cervical destructive spondylarthropathy (DSA), trigger finger and amyloid-filled bone cysts in the femoral neck area] were collected from the patient records at our hospital. The serum levels of C-reactive protein (CRP) and albumin and the use of erythropoiesis-stimulating agents (ESA) were also examined as parameters of malnutrition and inflammation.

Patients were divided according to gender and age as of the start of dialysis therapy (30 years and over, and under 30 years). The Kaplan–Meier test was used to estimate the history of operation and a log-rank test was used to compare the history of operations between the two groups. The Student t-test was used to compare continuous variables between the two groups. The chi-square or Fisher exact probability test was applied for categorical data. Data values are presented as the means ± SD. A probability of <0.05 was considered significant. All statistical calculations were performed using Stat View SE.

Results

Background characteristics of the long-term haemodialysis patients

Table 1 shows the characteristics of the patients, age, gender and the primary cause of their end-stage kidney disease (ESKD). Mean age was 62.5 ± 6.8 in the ‘30+’ group and 65.2 ± 7.1 in the ‘20–30’ group. Mean age at the start of haemodialysis was younger in ‘30+’ group (29.1 ± 7.3) than in ‘20–30’ group (40.5 ± 8.2, P = 0.0003). The mean duration of haemodialysis was 33.4 ± 1.9 years in the ‘30+’ group years and 24.7 ± 3.4 in the ‘20–30’ group. Out of 21 patients, 14 patients were male (66.7%) in the ‘30+’ group. All of their primary cause of ESKD was chronic glomerular nephritis in the ‘30+’ group, and all except one patient whose cause of ESKD was diabetic nephropathy was also chronic glomerular nephritis in ‘20–30’ group. Five patients (23.8%) were treated with HDF in the ‘30+’ group and five patients (38.5%) in ‘20–30’ group. The serum level of CRP tended to be higher and that of albumin tended to be lower in the ‘30±’ group than in the ‘20–30’ group, but the difference was not statistically significant. The rate of use of ESA tended to be higher in the ‘30+’ group than in the ‘20–30’ group, but this difference was also not statistically significant.

Operations for amyloidosis

Figure 1 shows the history of operations performed for CTS. Endoscopic carpal tunnel release was performed instead of conventional open carpal tunnel release after 1986. Among the 21 patients in the ‘30+’ group, 17 (81.0%) underwent operations for CTS at 30 years after the start of haemodialysis therapy (Figure 1a). No gender differences (Figure 1b) were observed. Patients who were 30 years and over at the start of their dialysis therapy underwent CTS operations more frequently than those who were under 30 years at the start of haemodialysis (100% versus 76.9%, respectively; P = 0.025, Figure 1c).

Figure 2 shows the history of operations performed for cervical DSA (decompression and fixation). Among the 21 patients in the ‘30+’ group, 6 (28.6%) underwent operations for cervical DSA at 30 years after the start of haemodialysis therapy (Figure 2a). No gender differences (Figure 2b) were observed. Patients who were 30 years and over at the start of their dialysis therapy underwent operations for cervical DSA more frequently than those who were under 30 years at the start of haemodialysis (62.5% versus 7.7%, respectively; P = 0.003, Figure 2c).

Figure 3 shows the history of operations performed for trigger finger and amyloid-filled bone cysts in the femoral neck area. Releasing the A1 pulley was performed for trigger finger, while a bipolar hemiarthroplasty was performed

<table>
<thead>
<tr>
<th>Duration of haemodialysis</th>
<th>20–30 years</th>
<th>Over 30 years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>13</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65.2 ± 7.1</td>
<td>62.5 ± 6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Age at the start of HD</td>
<td>40.5 ± 8.2</td>
<td>29.1 ± 7.3</td>
<td>0.0003</td>
</tr>
<tr>
<td>Duration of HD (years)</td>
<td>24.7 ± 3.4</td>
<td>33.4 ± 1.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>8 (61.5%)</td>
<td>14 (66.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Women</td>
<td>5 (38.5%)</td>
<td>7 (33.3%)</td>
<td>NS</td>
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<tr>
<td>Cause of ESKD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Chronic glomerulonephritis</td>
<td>12 (92.3%)</td>
<td>21 (100%)</td>
<td>NS</td>
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<tr>
<td>Diabetic nephropathy</td>
<td>1 (7.7%)</td>
<td>0 (0%)</td>
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<td>Method of haemodialysis</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>HD</td>
<td>8 (61.5%)</td>
<td>16 (76.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>HDF</td>
<td>5 (38.5%)</td>
<td>5 (23.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Parameters of malnutrition and inflammation</td>
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<td></td>
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<tr>
<td>CRP (mg/dl)</td>
<td>0.16 ± 0.08</td>
<td>0.33 ± 0.46</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.9 ± 0.2</td>
<td>3.8 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Use of ESA (%)</td>
<td>69.2</td>
<td>85.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

ESKD: end-stage kidney disease, CRP: C-reactive protein, ESA: erythropoiesis-stimulating agents, HD: haemodialysis, HDF: haemodiafiltration. Mean ± SD.
Characteristics of dialysis-related amyloidosis in patients on haemodialysis therapy for more than 30 years

Fig. 1. History of operations for carpal tunnel syndrome (CTS). (a) Overall patients (b) divided according to gender, (c) divided according to age at the start of HD.

Fig. 2. History of operations for cervical destructive spondyloarthropathy (DSA). (a) Overall patients, (b) divided according to gender, (c) divided according to age at the start of HD.

For amyloid-filled bone cysts in the femoral neck area. Among the 21 patients in the ‘30+’ group, 6 (28.6%) had undergone operations for trigger finger at 30 years after the start of haemodialysis therapy (Figure 3a). Among the 21 patients in the ‘30+’ group, 4 (19.0%) had undergone operations for amyloid-filled bone cysts in the femoral neck area at 30 years after the start of haemodialysis therapy (Figure 3b).
Figure 3. History of operations for other amyloidosis-related diseases. (a) Operations for trigger finger, (b) operations for amyloid-filled bone cysts in the femoral neck area.

Figure 4. Comparison of the history of operations for amyloidosis between haemodialysis for over 30 years and for 20–30 years’ age groups. (a) Operations for carpal tunnel syndrome, (b) operations for cervical destructive spondyloarthropathy, (c) operations for trigger finger, (d) operations for amyloid-filled bone cysts in the femoral neck area.

Figure 4 compares the operation histories for amyloidosis in the ‘30+’ and ‘20–30’ groups. No statistical differences were found between ‘30+’ group and ‘20–30’ group with regard to operations for CTS (23.8% versus 23.1%, respectively), trigger finger (9.5% versus, 15.4%, respectively) or amyloid-filled bone cysts in the femoral neck area (4.8% versus 7.7%, respectively) at 20 years after the start of haemodialysis therapy. None of the patients in the ‘20–30’ group had undergone an operation for cervical DSA at 20 years after the start of haemodialysis therapy.

We compared patients in whom haemodialysis had been started over the age of 40 years. Patients in the ‘30+’ group underwent operations for CTS more frequently than those in
the ‘20–30’ group at 20 years after the start of haemodialysis therapy [100% (2/2) versus 14.3% (1/7), respectively; \( P = 0.018 \). No statistically significant differences were found with regard to the mean age at the start of haemodialysis therapy between the ‘30+’ group (45.0 ± 2.8) and the ‘20–30’ group (46.3 ± 4.2).

**Discussion**

Dialysis-associated amyloidosis is one of the most serious complications associated with long-term haemodialysis. Beta 2-m-derived amyloid deposits on the bone, cartilage or synovia can cause CTS, trigger finger, DSA or cystic bone disease [4]. According to an overview of dialysis treatment in Japan, the rate of operations for CTS was 60.3% in patients receiving haemodialysis for more than 25 years [5]. No reports have described patients receiving haemodialysis therapy for more than 30 years. In the present report, 85.7% of the patients in the ‘30+’ group had undergone an operation for CTS, 28.6% had undergone an operation for trigger finger, 28.6% had undergone an operation for cervical DSA and 19.0% had undergone an operation for amyloid-filled bone cysts in the femoral neck area at 30 years after the start of haemodialysis therapy. Thus, haemodialysis-associated amyloidosis is common in patients receiving maintenance haemodialysis for more than 30 years.

Patients who were 30 years and over at the start of haemodialysis therapy underwent CTS and cervical DSA operations more frequently (100%, 62.5%, respectively) than those who were under the age of 30 years at the start of haemodialysis (76.9%, \( P = 0.025 \); 7.7%, \( P = 0.003 \), respectively) in the ‘30+’ group. Thus, older age at the start of haemodialysis was a risk factor for amyloidosis, similar to the results of previous studies [6–9]. The reason why a patient’s age at the onset of haemodialysis therapy is a risk factor for \( \beta \)-m amyloidosis is unclear. Jadoul et al. hypothesized that an increasing patient age might also increase the \( \beta \)-m load, possibly increasing the risk of \( \beta \)-m amyloidosis [10].

Since \( \beta \)-m, with a molecular weight of 11.800 Da, was first identified in 1985 as a major constituent protein of amyloid [4], haemodialysis technology for dialysis-related amyloidosis has been developed. Dialysis using high-flux membranes has been increasingly used in Japan since then. High-flux membranes or high-performance membranes remove larger molecular weight solutes, including \( \beta \)-m, with better biocompatibility than conventional unsubstituted cellulosic membranes [11–14]. The relative risk of CTS was reduced to 0.503 (\( P < 0.05 \)) and the mortality was reduced to 0.613 (\( P < 0.05 \)) for haemodialysis using high-flux membranes, compared with that using conventional membranes [15]. High-flux membranes substantially decreased the risk of morbidity and mortality [12]. The use of reverse osmosis water also became widely used at the same time. Schwalbe et al. reported that haemodialysis patients receiving water treated with demineralization or water softeners had a significantly higher rate of CTS and bone cyst than those receiving reverse osmosis water [16]. Reverse osmosis treatment for dialysis water was started in 1988 in our hospital, and high-flux membranes began to be used at almost the same time. Even though the mean age at the start of haemodialysis was younger in the ‘30+’ group than in the ‘20–30’ group, the frequency of operations for CTS, trigger finger and amyloid-filled bone cysts in the femoral neck area was not significantly different between the ‘30+’ group and the ‘20–30’ group at 20 years after the start of the maintenance haemodialysis therapy. The frequency of surgery for CTS was significantly higher in the ‘30+’ group than in the ‘20–30’ group among the patients in whom haemodialysis therapy was started over the age of 40 years. This may be attributable to recent advances in haemodialysis technologies, including the use of high-flux membranes and reverse osmosis water.

Haemodialysis-associated amyloidosis was common in patients receiving haemodialysis therapy for more than 30 years, especially among relatively older patients at the start of haemodialysis therapy. Even though the mean age at the start of haemodialysis was younger in the ‘30+’ group than in the ‘20–30’ group, the frequency of operations for amyloidosis did not differ between the ‘20–30’ and ‘30+’ groups at 20 years after the start of haemodialysis therapy. This trend might be explained by recently developed haemodialysis technologies, such as high-flux membranes and reverse osmosis water.

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**Conflict of interest statement.** None declared.

**References**

Frequencies of hepatitis B and C infections among haemodialysis and peritoneal dialysis patients in Asia-Pacific countries: analysis of registry data

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Abstract

Background. The impact of dialysis modality on the rates and types of infectious complications has not been well studied. The aim of the present investigation was to evaluate the rates of hepatitis C virus (HCV) and hepatitis B virus (HBV) infections in peritoneal dialysis (PD) and haemodialysis (HD) patients in the Asia-Pacific region.

Methods. The study included the most recent period-prevalent data recorded in the national or regional dialysis registries of the 10 Asia-Pacific countries/areas (Australia, New Zealand, Japan, China, Taiwan, Korea, Thailand, Hong Kong, Malaysia and India), where such data were available. Longitudinal data were also available for all incident Australian and New Zealand patients commencing dialysis between 1 April 1995 and 31 December 2005. Rates of HCV and HBV infections were compared by chi-square, Poisson regression and Kaplan–Meier survival analyses, as appropriate.

Results. Data were obtained on 201,590 patients (HD 173,788; PD 27,802). HCV seroprevalences ranged between 0.7% and 18.1% across different countries and were generally higher in HD versus PD populations (7.9% ± 5.5% versus 3.0% ± 2.0%, P = 0.01). Seroconversion rates on dialysis were also significantly higher in HD patients (incidence rate ratio PD versus HD 0.33, 95% CI 0.13–0.75). HCV infection was highly predictive of mortality in Japan (relative risk 1.37, 95% CI 1.15–1.62, P = 0.003) and in Australia and New Zealand (adjusted hazards ratio 1.29, 95% CI 1.05–1.58). HBV infection data were limited, but less clearly influenced by dialysis modality.

Conclusions. Dialysis modality selection significantly influences the risk of HCV infection experienced by end-stage renal failure patients in the Asia-Pacific region. No such association could be identified for HBV infection.

Keywords: end-stage renal failure; environmental transmission; haemodialysis; hepatitis B; hepatitis C