Prevalence of histological β2-microglobulin amyloidosis in CAPD patients compared with hemodialysis patients

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Background. The prevalence of β2-microglobulin amyloidosis (Aβ2m) in patients on continuous ambulatory peritoneal dialysis (CAPD) is unknown.

Methods. We prospectively obtained a median of 2 (range 1 to 4) joint samples from 26 CAPD patients aged 44 to 93 (median 73) years at post-mortem evaluation after 4.5 to 126 (median 27) months solely on CAPD (N = 19) or primarily on CAPD (that is, ≤ 10% and ≤ 1 year of renal replacement therapy time on other modalities; N = 7). The diagnosis of Aβ2m rested on Congo red staining (typical birefringence) and positive immunostaining of amyloid deposits by a monoclonal anti-β2m antibody.

Results. Aβ2m was diagnosed in 8 of 26 patients (31%). Prevalence ranged from 20% (2 of 10 patients) within ≤ 24 months CAPD to 30% (3 of 10 patients) after 24 to 48 months and 50% (3 of 6 patients) after 49 to 126 months (P = 0.11). The prevalence of Aβ2m was similar in patients without or with one or more peritonitis episodes. No significant difference in prevalence (P = 0.118) was found between CAPD patients (8/26; 31%) and hemodialysis patients (13/26; 50%) carefully matched for time on dialysis and age at the onset of dialysis.

Conclusions. The prevalence of histological Aβ2m reaches 31% after a median duration of 27 months of CAPD. This prevalence is not significantly different from that observed in a group of HD patients matched for age and dialysis duration.

Symptomatic β2-microglobulin amyloidosis (Aβ2m) has been reported occasionally in patients treated solely by continuous ambulatory peritoneal dialysis (CAPD) [1, 2]. Yet, its actual prevalence remains to be defined: clinical evidence of Aβ2m usually develops over a period of 10 years [3], a delay largely exceeding the average technical survival of CAPD [4]. In the absence of precise information on the prevalence of Aβ2m in CAPD, it has not been possible to ascertain whether peritoneal dialysis delays the onset of Aβ2m when compared with hemodialysis (HD).

We recently demonstrated in a prospective autopsy study of patients on chronic HD that histological evidence preceded clinical manifestations of Aβ2m by several years [5]. We take advantage of this new approach to define the prevalence of Aβ2m in CAPD patients and to compare it with that observed in HD subjects.

In the present prospective study of 26 patients treated by CAPD for a median of 27 months, Aβ2m was detected in 8 patients (31%). This prevalence was much higher than hitherto appreciated and did not differ significantly from that observed in a group of HD patients matched for age and duration of dialysis.

METHODS

CAPD patients

Inclusion criteria. All patients who died while on CAPD in participating units were submitted to a post-mortem examination (unless refused by families). Inclusion started in September 1988 in the co-ordinating center and in July 1992 in the other centers. Samples obtained up to May 31, 1997 are included in this report. Patients who had been treated for more than 10% and/or more than one year of the time on renal replacement therapy by another modality (HD, renal transplantation) were not included [5, 6]. One patient was excluded because of inadequate joint samples.

Patient characteristics. A total of 26 patients (18 males) were included. Their ages ranged from 36 to 91 (median 69) years at dialysis onset and from 44 to 93 (median 73) years at death. Total dialysis duration ranged from 4.5 to 126 months (median 27). Nineteen patients had been on CAPD only, while the 7 others had received an additional 0.5 to 8 months of HD (median 1).

The cause of end-stage renal failure was nephrosclerosis (N = 10), diabetic nephropathy (N = 6), amyloidosis (N = 1).
4), chronic glomerulonephritis (N = 4), autosomal dominant polycystic kidney disease (N = 1), and unknown (N = 1).

A median of 1 (range 0 to 8) peritonitis episode was recorded per patient throughout follow-up.

One single patient had undergone carpal tunnel syndrome (CTS) surgery prior to the onset of CAPD.

Statistical analysis

The prevalence of $\beta_2$-microglobulin amyloidosis in CAPD and HD patients was compared by calculating an odds ratio (OR) for matched studies. The significance was assessed using the Logit-Woolf method.

$P$ values < 0.05 were considered to be significant.

RESULTS

Histological prevalence of $\beta_2$-m in CAPD patients

$\beta_2$-m was diagnosed in 8 of 26 patients (31%), as early as within 21 months CAPD. The prevalence ranged from 20% (2 of 10 patients) after 1 to 24 months to 30% (3 of 10 patients) after 25 to 48 months and 50% (3 of 6 patients) after 49 to 126 months CAPD ($P = 0.11$, Armitage test for increasing trend in prevalences)

Inclusion of the few months of HD treatment did not modify these results.

Histological $\beta_2$-m and previous CTS surgery

The single patient who underwent CTS surgery had no $\beta_2$-m amyloid deposits in the tissue removed during CTS surgery or in the joints after 25 months CAPD.

Histological $\beta_2$-m and amyloidosis as a cause of end-stage renal failure

Renal amyloidosis was the cause of ESRD in four patients who dialyzed respectively for 8, 25, 29 and 126 months. Evidence of $\beta_2$-m was present only in the latter patient.

Histological $\beta_2$-m and number of peritonitis episodes

The prevalence of $\beta_2$-m was similar in patients without an episode (3 of 9, 33%), with one episode (3 of 7, 43%) or more than one episode (2 of 10, 20%).

Comparison of $\beta_2$-m prevalence in CAPD and HD patients

As shown in Table 1, age and time on dialysis were not different in CAPD patients and in matched HD patients.

The prevalence of $\beta_2$-m was not significantly different between the two groups: 31% (8 of 26) and 50% (13 of 26) in CAPD and HD patients, respectively (OR 3.5; 95% CI 0.73 and 16.7; $P = 0.118$).

No significant difference was found even between subgroups of CAPD and HD patients with a similar dialysis duration (Table 2).

DISCUSSION

Our data quantify for the first time, to our knowledge, the prevalence of $\beta_2$-m in patients treated exclusively or
Table 2. Prevalence of \( \beta_2 \)-m as a function of time on dialysis in CAPD and matched HD patients

<table>
<thead>
<tr>
<th>Months on dialysis</th>
<th>CAPD patients</th>
<th>HD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–24</td>
<td>2+ /10 (20%)</td>
<td>2+ /10 (20%)</td>
</tr>
<tr>
<td>25–48</td>
<td>3+ /10 (30%)</td>
<td>6+ /10 (60%)</td>
</tr>
<tr>
<td>49–156</td>
<td>3+ /10 (50%)</td>
<td>5+ /6 (83%)</td>
</tr>
</tbody>
</table>

Abbreviations are: \( \beta_2 \)-m, \( \beta_2 \)-microglobulin amyloidosis; CAPD, continuous ambulatory peritoneal dialysis; HD, hemodialysis.

almost exclusively by CAPD. Surprisingly, the prevalence of \( \beta_2 \)-m had already reached 20% within the first two years of therapy. The overall prevalence in patients followed for 4.5 to 126 months on CAPD reached 31%. The 50% prevalence of \( \beta_2 \)-m observed in the 49 to 156 month group suggests that improvements in the technical survival of CAPD will be accompanied by a rising incidence of symptomatic \( \beta_2 \)-m.

These results may be taken as representative of the prevalence of joint \( \beta_2 \)-m. Indeed, at least one sternalclavicular joint sample, reputed for its sensitivity (97%) in the detection of joint \( \beta_2 \)-m [5], was obtained from all CAPD patients in whom no \( \beta_2 \)-m was detected, except one. Just as in HD [5], histological evidence precedes the clinical symptoms of \( \beta_2 \)-m by several years.

Until now, the actual prevalence of \( \beta_2 \)-m in patients on CAPD could not be calculated. Indeed, the clinical manifestations used to assess \( \beta_2 \)-m (CTS and bone cysts) develop late after the onset of renal replacement therapy [3]. The short technical survival of CAPD [4] therefore precludes a precise assessment of the prevalence of \( \beta_2 \)-m.

The present results permit to compare the prevalence of \( \beta_2 \)-m in patients treated by CAPD and HD. The comparison is reliable. Indeed, the same method was used to detect \( \beta_2 \)-m in joints obtained at autopsy during the same time interval. Furthermore, in this study the CAPD and HD patients were carefully matched for age at the onset of dialysis and time on dialysis, two major risk factors for \( \beta_2 \)-m [5, 6].

Although prevalence is identical in the two groups within the first years of dialysis, it tends to be lower subsequently in the CAPD population, without reaching statistical significance. Overall, for the same duration of treatment, prevalence reached 31% in the CAPD versus 50% in the HD group. The lack of statistical significance of this difference might be related to the limited size of the population, that is, a \( \beta \)-type statistical error. It may be calculated that the sample size should increase to over 50 patients in each group for statistical significance to be reached. At any rate the present data suggest that the actual difference should not exceed 20%.

Patients on CAPD were expected to have a lower prevalence of \( \beta_2 \)-m than those on HD as a result of their lower serum \( \beta_2 \)-m levels [7, 8]. Of note, the only study claiming that serum \( \beta_2 \)-m levels were similar in CAPD and HD patients failed to match them for residual renal function (or diuresis) [9], which is a major determinant of the serum \( \beta_2 \)-m level [10].

Two clinical studies have compared the prevalence of clinical manifestations of \( \beta_2 \)-m in CAPD and HD patients [11, 12]. Each study had shortcomings and the conclusions were contradictory. Nomoto et al reported a very low prevalence of CTS (0.14%) in a population of 5050 CAPD patients [11]. However, they failed to compare these results with an appropriately matched group of HD patients. In addition, the likelihood of CTS being due to \( \beta_2 \)-m is limited by the fact that \( \beta_2 \)-m was demonstrated in only one of the seven CTS cases, all of whom were females known to be at high risk of CTS in the absence of uremia [13]. Detailed evaluation of these results is further hampered as neither mean age, mean duration on CAPD, nor the time possibly spent on HD were provided in this paper [11].

Benz, Siegfried and Teehan concluded that there was no difference in the prevalence of CTS, evaluated by nerve conduction studies, between 90 HD and 61 CAPD treated patients: 18% and 14% of the patients had nerve conduction abnormalities after a mean follow-up of 51.6 and 33.8 months on HD and CAPD, respectively [12]. However, the average age of both groups at the onset of dialysis was not mentioned.

Schwalbe et al recently reported a profound drop in the prevalence of \( \beta_2 \)-m in their HD patients between 1988 and 1996 [14]. They speculated that this fall reflected recent improvements in dialysate purity and their attendant reduction in intraclinical inflammatory stimuli [14]. In our study, despite the use of sterile pyrogen-free peritoneal dialysate, \( \beta_2 \)-m affected nearly one third of patients on dialysis for a median of 27 months only. This suggests that dialysate purity is not a major determinant of \( \beta_2 \)-m prevalence and that alternative explanations should be considered for Schwalbe et al’s observations. The lack of an association between the number of peritonitis episodes and \( \beta_2 \)-m prevalence in our CAPD cohort fits with this suggestion. It should be noted, however, that peritoneal dialysis may be associated with systemic monocyte activation [15] that may contribute to \( \beta_2 \)-m genesis even in peritonitis-free patients.

In conclusion, the histological prevalence of joint \( \beta_2 \)-m reaches 31% (8 of 26) after a median of 27 months CAPD, a much higher number than hitherto appreciated. It is not significantly different from that observed in a group of HD patients matched for age and time on dialysis.

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