Alport syndrome and encapsulating peritoneal sclerosis (EPS) are both rare diseases. Their joint occurrence is highly unlikely. Two patients at our center with Alport syndrome developed EPS. We therefore hypothesized that Alport syndrome might predispose to the development of EPS and that this predisposition might be reflected in a fast peritoneal transport rate at baseline.

We compared the mass transfer area coefficient (MTAC) of creatinine and the clearances of albumin, immunoglobulin G, and α₂-macroglobulin at baseline and for all subsequent available measurements in four patient groups: EPS patients with Alport syndrome, EPS patients without Alport syndrome, Alport patients without EPS, and long-term peritoneal dialysis (PD) patients without EPS. The transport characteristics were obtained during a standard peritoneal permeability analysis.

Between July 1995 and December 2008, 5 of 417 PD patients treated at our center had Alport syndrome as their primary kidney disease, and 13 of the 417 developed EPS. Of those 13 EPS patients, 2 had Alport syndrome. We observed no differences in the baseline transport characteristics of the four groups under consideration. Taking all measures of transport characteristics into account, only the MTAC of creatinine was higher in the two EPS groups than in the other two groups (p = 0.01).

We could not confirm our hypothesis that Alport syndrome affects peritoneal solute clearances.

Key words
EPS, Alport syndrome, protein clearances

Introduction
Alport syndrome and encapsulating peritoneal sclerosis (EPS) are both rare conditions. Alport syndrome causes end-stage renal disease in 0.2% – 5% of incident dialysis patients (1). Encapsulating peritoneal sclerosis is estimated to occur in approximately 2.7% of peritoneal dialysis (PD) patients in the Netherlands (unpublished data). The joint manifestation of these conditions would therefore seem highly unlikely. However, in a recent study performed by our group, 2 of 13 patients with EPS had Alport syndrome as their primary kidney disease (2).

Alport syndrome is a rare disorder of collagen IV, which is present in basement membranes throughout the body (3). Whether Alport syndrome affects the basement membrane of the peritoneal tissues and vessels, causing protein leakage, is unknown. In a case report from the early days of acute PD, a patient with Alport syndrome was described as having excessive peritoneal protein loss (4). Encapsulating peritoneal sclerosis is a severe complication of long-term PD (5). It is usually associated with increased solute clearances.

We hypothesized that Alport syndrome affects the basement membrane of the peritoneal vessels, causing protein leakage. We therefore formulated this research question: Do patients with Alport syndrome, with and without EPS, have peritoneal protein clearances higher than those in other long-term PD patients?

Methods
All patients with Alport syndrome and all with EPS who were treated with PD between July 1995 and December 2008 at our center were selected for the present study. We compared baseline transport characteristics obtained during a standard peritoneal permeability analysis [SPA (6)] in

- EPS patients with Alport syndrome,
- EPS patients without Alport syndrome,
Alport syndrome patients without EPS, and
long-term PD patients without EPS and without Alport syndrome.

The SPA was considered “baseline” if done within the first 12 months from the start of PD treatment. Long-term PD patients had been on PD for at least 35 months, a restriction that was chosen based on the shortest PD duration in the group of Alport syndrome patients. The intention was to keep the PD duration between the groups similar.

At our center, PD patients undergo a SPA once annually. The SPA uses a 4-hour dwell with a 3.86% glucose-based dialysis solution as previously described (7). For the present study, we investigated the mass transfer area coefficient (MTAC) of creatinine and the peritoneal clearances of albumin (Alb), immunoglobulin G (IgG), and α₂-macroglobulin (A2M) at baseline. We also compared all subsequent measurements of MTAC creatinine and clearances of Alb, IgG, and A2M.

The statistical analysis used the chi-square and Kruskal–Wallis tests as appropriate.

Results
Between July 1995 and December 2008, 417 PD patients were treated at our center. Five of those PD patients had Alport syndrome (1%). Thirteen PD patients developed EPS during that period (3%). Two of the 13 patients with EPS had Alport syndrome (15%). Table I gives the patient characteristics.

Baseline SPAs were not available for all patients. Figure 1 shows the baseline MTAC of creatinine and the baseline clearances of Alb, IgG, and A2M in the four patient groups. We observed no differences between the groups. Figure 2 shows all measurements of MTAC creatinine and all clearances of Alb, IgG, and A2M. The MTAC creatinine was higher in the two EPS patient groups than in the other two groups (p < 0.01).

Discussion
Clearances and solute transport rates, whether at baseline or in total, were not higher in patients with Alport syndrome than in other PD patients. Therefore, the results of this study could not confirm our hypothesis that Alport syndrome affects the basement membrane of peritoneal vessels, causing protein leakage. Encapsulating peritoneal sclerosis is often associated with fast transport of small solutes, and that association was confirmed in our study (8,9).

We observed no differences in protein clearances between the various patient groups. That finding contrasts with the data for an Alport patient described in the past (4), suggesting that the stability of peritoneal collagen IV is maintained by compensatory mechanisms. The next few paragraphs put forward a hypothesis about the possible pathophysiologic mechanisms.

The various collagen IV chains are linked, forming collagen IV networks. Those networks are the major constituents of basement membranes and serve as a scaffolding for the deposition of other matrix glycoproteins and for the attachment of cells. All basement membranes contain alpha-1 and -2 collagen IV chains. Some specialized basement membranes—for instance, the glomerular basement membrane (GBM)—also contains alpha-3 to -6 chains (10–12).

Most patients with Alport syndrome have a deletion in the X chromosome leading to a complete or segmental loss of the alpha-5 chain, normally present in the GBM, the eye lens, the cochlea, and the skin (3). Collagen IV stability is therefore less in the above-mentioned organs, resulting in the well-known renal, cochlear, and ocular symptoms of Alport syndrome.

Yet, patients with Alport syndrome have no skin abnormalities. This lack may be explained by increased deposition of collagen VII, which is likely to compensate for the absence of the stabilizing activity normally exerted by alpha-5 collagen IV chains (13).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alport syndrome and EPS</th>
<th>No EPS</th>
<th>EPS and no Alport syndrome</th>
<th>Long-term PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>2</td>
<td>3</td>
<td>11</td>
<td>135</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>2/0</td>
<td>2/1</td>
<td>5/6</td>
<td>79/56</td>
</tr>
<tr>
<td>Age at PD start (years)</td>
<td>16, 30</td>
<td>22, 36, 38</td>
<td>24 (9–68)</td>
<td>46 (6–81)</td>
</tr>
<tr>
<td>Total PD duration (months)</td>
<td>66, 128</td>
<td>35, 50, 54</td>
<td>79 (55–149)</td>
<td>50 (35–107)</td>
</tr>
</tbody>
</table>

a For groups of 3 or fewer patients, individual values are given; for larger groups, median and range are presented. EPS = encapsulating peritoneal sclerosis; PD = peritoneal dialysis.
general, collagen VII is involved in wound healing and the formation of scars. In the kidney, it is present in sclerosed glomeruli. The presence of collagen VII has been demonstrated in the retina (14). The abnormalities of the peritoneum found in long-term PD resemble those in the retinas of patients with proliferative diabetic retinopathy, which may therefore suggest the presence of collagen VII in the peritoneum (15). The absence of alpha-5 collagen IV chains or the presence of collagen VII in the peritoneum of patients with Alport syndrome is unknown.

The other 3 patients at our center with Alport syndrome did not develop EPS despite having long PD durations. First, EPS is multifactorial. Therefore the development of EPS cannot be explained by a single factor. Second, the magnitude of the deletion of the specific genes may influence the presentation of the disease. The clinical presentation of Alport syndrome depends on the type of mutation and on the size of the deletion in the COL4A3, COL4A4, or COL4A5 gene. We speculate that the mutation type may influence the development of EPS.

**Conclusions**

We need to be prudent in drawing conclusions from our small cohort. We could not demonstrate the involvement of Alport syndrome in protein leakage. Further studies should focus on the survival of PD patients with Alport syndrome in various registries and on an analysis of collagen IV and VII in peritoneal tissue.
References


FIGURE 2 Box-and-whisker plots of all measurements in peritoneal dialysis (PD) patients of the mass transfer area coefficient (MTAC) of creatinine (left upper panel) and peritoneal clearances of albumin [Cl Alb (right upper panel)], immunoglobulin G [Cl IgG (left lower panel)], and $\alpha_2$-macroglobulin [A2M (right lower panel)] for 4 groups: encapsulating peritoneal sclerosis (EPS) patients with Alport syndrome, EPS patients without Alport syndrome, Alport syndrome patients without EPS, and long-term PD patients without EPS and without Alport syndrome. The numbers below the horizontal axis represent the number of patients and the number of measurements in each group. The MTAC of creatinine was higher in both EPS patient groups than in the other two groups ($p < 0.01$).


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