Encapsulating peritoneal sclerosis in paediatric peritoneal dialysis patients: the experience of the Italian Registry of Pediatric Chronic Dialysis

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ABSTRACT

Background. Paediatric literature about encapsulating peritoneal sclerosis (EPS) is limited and comes primarily from anecdotal experiences. In this study, we described the incidence and characteristics of EPS in a large paediatric chronic peritoneal dialysis (CPD) patient population.

Methods. We reviewed files of patients starting CPD at <16 years of age, recorded from January 1986 to December 2011 by the Italian Registry of Pediatric Chronic Dialysis (n = 712). Moreover, in December 2011, a survey was performed involving all the Italian Pediatric Nephrology Units to report such EPS cases that occurred after CPD withdrawal.

Results. Fourteen EPS cases were reported, resulting in a prevalence of 1.9%. The median age of EPS cases was 4.8 years (range 0.6–14.4) at the start of CPD and 14.3 years (6.5–26.8) at EPS diagnosis. Eleven EPS cases received CPD for longer than 5 years. At diagnosis, nine patients were still on CPD, two were on haemodialysis and three were transplanted. In eight patients, the primary renal disease was represented by glomerulopathy, mainly focal segmental glomerulosclerosis (n = 5). In the last 6 months prior to CPD discontinuation, 10 patients were treated with solutions containing more than...
INTRODUCTION

Peritoneal dialysis (PD) represents the preferred chronic dialysis modality in paediatric age [1, 2]. Infections and growth failure are major problems in chronic PD (CPD) paediatric patients and have been extensively studied, while few data are available concerning the occurrence of encapsulating peritoneal sclerosis (EPS) in this age group. EPS is a rare but extremely serious long-term complication of CPD. Despite the growing attention that EPS has received during the last 10 years, its aetiology and pathogenesis are not yet understood entirely, and clinical issues such as epidemiology, diagnosis and treatment still need clarification. In adults, the reported prevalence of this condition ranges from 0.5 to 7.3% [3], while reports on EPS in children are rare. Hoshii et al. [4] first reported the characteristics of paediatric patients with EPS in Japan, describing 11 cases among 687 patients enrolled in the Japanese paediatric dialysis registry, which corresponds to a prevalence of 1.6%. Ekim et al. [5] reported a single-centre Turkish experience of two patients diagnosed with EPS among 104 paediatric dialysis patients followed over a 14-year period, resulting in a prevalence of 1.9%. Recently, two paediatric case reports described the occurrence of EPS shortly after kidney transplantation [6, 7].

The aim of this study was to investigate the incidence, characteristics and possible risk factors of EPS in a large national registry population of paediatric CPD patients.

MATERIALS AND METHODS

We retrospectively reviewed the files of patients starting CPD before the age of 16 years, recorded from January 1986 to December 2011 by the Italian Registry of Pediatric Chronic Dialysis, a nationwide permanent chronic dialysis network involving all 12 Italian paediatric dialysis centres. Moreover, in December 2011, a questionnaire was sent to all the Italian Pediatric Nephrology Units aimed at reporting EPS cases that occurred after PD withdrawal. The response rate to the questionnaire was 100% as a reply was requested from all the Units even if no such EPS cases had occurred.

The diagnosis of EPS was based on the definition by the ISPD [3], which defined EPS as a clinical syndrome characterized by signs and symptoms of obstructive ileus with peritoneal thickening and encapsulation, intestinal obstruction, cocooning and/or peritoneal calcifications confirmed by radiological investigations, macroscopic or histopathological findings. The incidence of EPS was calculated as the number of EPS cases by the number of patients at risk in the same time period. Peritonitis incidence was 1:26.8 CPD-months, similar to that calculated in children >12 months of age from the same registry (1:28.3 CPD-months). The mortality rate was 43%. A more aggressive course and an association with calcineurin inhibitors were observed in transplanted patients.

Conclusions. Surveillance for EPS should be maintained in high-risk children who received long-term PD even after years from CPD withdrawal.

RESULTS

Clinical characteristics and possible risk factors

Over a 25-year period, 712 patients aged 16 years or less at the start of chronic dialysis (median age 6.4 years; range 0.1–16 years) were treated with PD in 12 dialysis centres. The median duration of the first CPD cycle was 17.7 months (range 1–198 months) and 52 patients (7.3%) were treated for more than 5 years.

A diagnosis of EPS was made in 14 patients (1.9%) whose median age was 4.8 years (range 0.6–14.4) at the start of CPD and 14.3 years (range 6.5–26.8 years) at EPS diagnosis. EPS was diagnosed in seven patients between 1992 and 1999 and in seven patients between 2000 and 2008. No other EPS cases have been reported since then. Diagnoses leading to end-stage renal failure in EPS cases were primary glomerulopathies (n = 8), congenital anomalies of kidney and urinary tract (n = 4), cystinosis and renal lymphoma (1 case each). Five out of eight patients with glomerulopathies were affected by focal segmental glomerulosclerosis (FSGS). The incidence of EPS in the FSGS patients of our registry was 10.2%, while it was only 1.2% among the patients with other forms of primary renal disease.

The median CPD duration (not necessarily continuous) before EPS diagnosis was 84.7 months (range 51.7–138.8), significantly greater than that of the total registry population (24.7 months; P < 0.05). The incidence of EPS was 0.45% in children with a PD exposure <5 years (3/660) and 21.1% in those with a PD exposure ≥5 years (11/52). Nine EPS patients underwent a single course of CPD, whereas five patients underwent two courses. In EPS cases, there was no significant difference in the median CPD duration, whether the primary renal disease was or was not FSGS (82.4 versus 86 months, respectively).

EPS was diagnosed in five patients after a median time of 25.4 months (range 3–88) from PD withdrawal: two children were on haemodialysis (at 15.6 and 25.4 months from CPD discontinuation, respectively) and three patients were transplanted.

The most common symptoms and imaging findings for EPS are shown in Table 1. Most children complained of a clinical triad characterized by abdominal pain, vomiting and weight loss, without fever. Ten patients (71%) had a diagnostic imaging (ultrasound scan and/or computerized tomography) and the more pertinent findings for confirmation of EPS diagnosis were peritoneal membrane thickening, bowel adhesion and peritoneal calcification. When imaging was unavailable,
diagnosis of EPS was made on the basis of both clinical and pathology criteria (histology and gross findings at surgery).

Common histological findings of EPS were loss of mesothelial cell layer, fibrin deposition on the peritoneal surface and severe sub-mesothelial sclerosis >400 μm in thickness. Signs of severe vasculopathy were reported in four out of nine patients with biopsy-proven EPS. The histopathological findings of the peritoneal biopsies are summarized in Table 2.

During the PD treatment period, 10 out of 14 patients with EPS (71%) had no residual urine output (<0.5 mL/kg/h) and their mean ultrafiltration (UF) volume was <300 mL/m² body surface area per day in the last 6 months prior to CPD discontinuation. These 10 patients were on PD solutions containing more than 2.27% glucose to achieve ultrafiltration. All children were on lactate-buffered PD fluid and no patients were exposed to icodextrin during the CPD treatment period. The peritoneal equilibration test (PET) was available in 4 out of the 14 EPS cases. The test was performed about 6 months prior to EPS diagnosis and showed a high-transport status in all four cases (Table 3).

Forty-eight cases of peritonitis were reported in 12 patients; two patients had no history of peritonitis. The overall incidence was one episode every 26.8 CPD-months, which was not significantly different from that calculated in children >12 months of age from the same registry (1.283 CPD-months). The most commonly observed organisms were Gram-positive cocci (56%), followed by Gram-negative bacilli (12%) and Candida spp. (7%). Peritoneal effluent culture was negative in 4 of 48 episodes (8.3%).

We had access to antihypertensive therapy records for nine EPS cases only. While on CPD, seven cases (77%) were prescribed β-blockers (atenolol in four patients and carvedilol in three patients). The proportion of EPS cases receiving this antihypertensive drug was significantly greater than that reported in the total registry population (4%; P < 0.05).

### The post-transplantation EPS cases

Three EPS cases out of 14 (21.4%) had been transplanted before EPS diagnosis. All these patients had an acute illness presentation and course, with either acute intestinal obstruction or perforation; the renal grafts were still functioning when EPS was diagnosed. These cases had previously received a single course of CPD treatment with a median duration of 106.2 months (range 75.1–116.7). Diagnosis of EPS was made at 3, 17 and 88 months from PD discontinuation, respectively. All transplanted patients were on alternative-day prednisone and calcineurin inhibitor-based immunosuppressive regimen: cyclosporine A, cyclosporine A + mycophenolic acid and tacrolimus + mycophenolic acid (one case each). EPS clinical course was fatal in two out of three patients. In the most recently diagnosed patient (2009), clinical evolution was positive with still functioning renal graft at the end of the follow-up period. Episodes of recurrent abdominal pain or constipation are not reported. The estimated GFR is currently 80 mL/min/1.73 m² at 4.5 years after kidney transplantation and 3 years after EPS diagnosis.

### Treatment

Description of medical therapy was available for 9 out of 14 EPS patients. Corticosteroids were prescribed in six patients both in monotherapy or associated with tamoxifen or azathioprine (one case each). Current immunosuppressive regimen was maintained in two out of three post-transplant cases (prednisone + cyclosporine A, prednisone + tacrolimus + mycophenolic acid), whereas one patient was maintained on prednisone, while cyclosporine A and mycophenolic acid were discontinued with the introduction of sirolimus.

Six patients underwent laparotomy for acute surgical indication (complete intestinal obstruction). In these cases, a large enterolysis was performed; intestinal intubation and segmental colon resection were required in two patients. Three out of these six patients died after recurrent bowel perforations.

### Table 1: Main symptoms and radiological abnormalities found in the 14 cases of EPS

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>n</th>
<th>Imaging findings (US or CT scan)</th>
<th>n</th>
</tr>
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<tbody>
<tr>
<td>Abdominal pain</td>
<td>14</td>
<td>Peritoneal membrane thickening</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>Bowel adhesion or aggregation</td>
<td>6</td>
</tr>
<tr>
<td>Weight loss</td>
<td>9</td>
<td>Peritoneal calcification</td>
<td>5</td>
</tr>
<tr>
<td>Ascites</td>
<td>5</td>
<td>Loculated ascites</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>3</td>
<td>Gas-fluid levels</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3</td>
<td>Stenotic small bowel loops</td>
<td>3</td>
</tr>
<tr>
<td>ESA resistance</td>
<td>3</td>
<td>Dilated small bowel loops</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bowel wall thickening</td>
<td>2</td>
</tr>
</tbody>
</table>

US, ultrasound; CT, computerized tomography; ESA, erythropoiesis-stimulating agents.

### Table 2: Frequency of histological findings in nine EPS patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of mesothelial cell layer</td>
<td>9</td>
</tr>
<tr>
<td>Fibrin deposition on surface</td>
<td>7</td>
</tr>
<tr>
<td>Sub-mesothelial sclerosis</td>
<td>9</td>
</tr>
<tr>
<td>Cellular</td>
<td>4</td>
</tr>
<tr>
<td>Acellular</td>
<td>9</td>
</tr>
<tr>
<td>Inflammatory infiltrates</td>
<td>5</td>
</tr>
<tr>
<td>Acute</td>
<td>5</td>
</tr>
<tr>
<td>Chronic</td>
<td>1</td>
</tr>
<tr>
<td>Small-vessel walls thickening</td>
<td>4</td>
</tr>
<tr>
<td>Small-vessel narrowing/occlusion</td>
<td>4</td>
</tr>
<tr>
<td>Pt</td>
<td>Primary disease</td>
</tr>
<tr>
<td>----</td>
<td>----------------</td>
</tr>
<tr>
<td>1</td>
<td>FSGS</td>
</tr>
<tr>
<td>2</td>
<td>FSGS</td>
</tr>
<tr>
<td>3</td>
<td>CNS</td>
</tr>
<tr>
<td>4</td>
<td>CAKUT</td>
</tr>
<tr>
<td>5</td>
<td>FSGS</td>
</tr>
<tr>
<td>6</td>
<td>CAKUT</td>
</tr>
<tr>
<td>7</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>8</td>
<td>Cystinosis</td>
</tr>
<tr>
<td>9</td>
<td>FSGS</td>
</tr>
<tr>
<td>10</td>
<td>FSGS</td>
</tr>
<tr>
<td>11</td>
<td>IgAN</td>
</tr>
<tr>
<td>12</td>
<td>CNS</td>
</tr>
<tr>
<td>13</td>
<td>CAKUT</td>
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<td>14</td>
<td>CAKUT</td>
</tr>
</tbody>
</table>

FSGS, focal segmental glomerulosclerosis; CNS, congenital nephrotic syndrome; CAKUT, congenital anomaly of kidney and urinary tract; IgAN, IgA nephropathy; CsA, cyclosporin A; AZA, azathioprine; TAC, tacrolimus; MPA, mycophenolic acid.
Outcome

The overall mortality rate in our case series was 43%, significantly greater than that of the total registry population (2.3%). Death occurred shortly after PD withdrawal in one case (1 month) and while on haemodialysis in three patients, after 15.6, 17.8 and 25.4 months from PD discontinuation, respectively. EPS clinical course was also fatal in two out of three transplanted patients. All of the survivors were successfully maintained on haemodialysis (seven patients) or transplantation (one patient).

Discussion

Chronic PD can be complicated by EPS, which can be considered the most severe complication associated with long-term PD. Since 2000, EPS has received growing attention in Europe and a better characterization of this condition might have affected patient and clinician’s choice of renal replacement therapy [8]. There is now a flourishing literature about this topic in adult CPD patients, exploring incidence, risk factors, treatment and outcome of EPS [9-11]. On the other hand, due to EPS rarity, description in end-stage renal failure children receiving CPD is based upon few data and anecdotal experiences [5-7, 12, 13].

In this study, we present the clinical, radiological and histological data and outcome of 14 patients with EPS starting CPD at paediatric age. In addition to a paediatric multicentre case series [4], published 12 years ago, our survey provides comprehensive information obtained from a large nationwide registry and points to EPS as a still unsolved complication of CPD in children.

Our experience represents the largest paediatric case series ever reported, providing evidence of a wide variability in the timing of EPS onset also in children. Five out of 14 children were diagnosed several months after CPD discontinuation, when on haemodialysis (two cases) or already transplanted (three cases). In agreement to what has recently been reported in adults [14], EPS cases that occurred after CPD withdrawal were all characterized by an acute presentation with rapid clinical course, whereas while on CPD, the patients underwent a subacute presentation and course.

The time on PD was the most important risk factor for EPS due to the longer exposure of the peritoneum to the harmful effects of PD fluids [15]. Kawanishi et al. [16] reported a progressive increase in the overall incidence of EPS associated with the duration of PD: rates of EPS were 2.1% for patients receiving PD for 5–8 years and 17.2% for those few patients that were on PD for longer than 15 years. More recently, Brown et al. [17], on behalf of the Scottish Registry, reported a high incidence of EPS even with shorter PD duration, as they observed incidence rates of 2, 3.5, 8.1 and 8.8% after 2, 3, 4 and 5 years on continuous PD, respectively. As far as previous paediatric studies are concerned, Hoshii et al. [4] reported that patients who developed EPS had all received PD for longer than 5 years, with a mean CPD duration of 10.3 years. Moreover, in all the paediatric EPS case reports, CPD duration was between 4 and 10 years [5-7, 13]. Our study confirms the link between the duration of PD and the likelihood of EPS occurrence, as the median CPD duration was 7 years in the 14 EPS cases compared with ~2 years in the total population of children on PD.

Araki et al. [18] performed peritoneal biopsies in children who had received PD for more than 5 years to investigate how long CPD could be performed safely. Among 14 patients on CPD for a mean of 7.8 years, there were six patients with histological finding of simple sclerosis and eight patients with a greater degree of peritoneal sclerosis, along with evidence of inflammation and vasculopathy. In these eight cases, both peritoneal calcifications on abdominal computerized tomography scan and ultrafiltration failure (UFF) were observed at the time of histological diagnosis. Two out of eight patients developed EPS. The authors concluded that if a patient receives PD for more than 5 years and demonstrates both poor UF and peritoneal calcifications on computerized tomography scan, a peritoneal biopsy should be performed to rule out the presence of severe peritoneal sclerosis.

Although UFF can occur in any stage of CPD, it may worsen over time and is especially important in long-term PD [19]. UFF is caused mainly by a large vascular surface of peritoneal membrane that leads to an increased permeability [dialysate-to-plasma ratios for creatinine (D/Pcr) >0.80] and to faster glucose absorption. This can result in the need for high dialysate glucose concentrations that can further worsen both the peritoneal membrane structure and function [20]. In our study, a dialysate glucose concentration >2.27% was used in 71% of patients after the development of UFF. In Hoshii et al. case series [4], 4.25% glucose bags were used to achieve UF in 9 out of 11 patients with EPS (82%). Based on this observation, the authors suggested that cessation of CPD should be considered in children with no residual urine volume, UFF and receiving CPD with dialysate bags of high-glucose solution. As increased peritoneal membrane permeability itself may be a risk factor for EPS, the PET should be performed routinely, at least in children receiving long-term PD, and urea and creatinine D/P ratios, and glucose D/D0 ratio can be compared with the results from a large paediatric study in which the standard paediatric PET was adopted [21]. PET was performed only in 4 out of our 14 patients, while it would be advisable to regularly perform it along CPD treatment in order to timely register any change in peritoneal membrane transport characteristics.

Previous studies suggested that PD-related peritonitis might predispose to EPS, particularly if caused by Staphylococcus aureus, fungi or Pseudomonas aeruginosa [22, 23]. In our series, as in recent adult and previous Japanese studies [3, 9, 11, 17], the peritonitis rate of patients with EPS was not particularly high nor was it significantly different from that observed in the overall CPD paediatric population enrolled in the registry. It should be noted that, in calculating the peritonitis rate, we excluded neonates and infants, as it is well known that their dialysis treatment is characterized by a greater risk of infectious complications [1]. Therefore, the number of peritonitis did not seem to represent itself a risk factor for EPS, while a single severe acute episode of peritonitis is probably
sufficient to trigger the EPS pathophysiological cascade in an already impaired peritoneal membrane [24].

In 1974, Brown et al. first observed an association between EPS and β-blockers [25], but subsequent reports did not support this link [17, 26]. We found that many of our patients with EPS had a history of β-blocker administration (mainly atenolol and carvedilol). However, these patients were all severely hypertensive, mainly as a result of fluid retention, and they were all put into at least three different classes of antihypertensive drugs. Therefore, the clinical significance of β-blockers per se on the development of EPS cannot be demonstrated by the current study.

EPS may occur during treatment with CPD, after patient’s switch to haemodialysis or following kidney transplantation. Post-transplantation EPS occurs with increasing frequency in adults [27]. The majority of EPS cases are observed within a few years after transplantation, but some cases were diagnosed in transplanted patients many years after CPD discontinuation [14]. In recently published paediatric reports, two children developed signs of severe bowel obstruction 3 and 8 months after undergoing a kidney graft, respectively [6, 7]. In our case series, two out of the three post-transplant EPS cases occurred nearly 1.5 and 7 years after kidney transplantation. All three patients were on calcineurin inhibitor-based immunosuppressive regimen. Based on our results, a prolonged clinical vigilance for the diagnosis of EPS is warranted even after kidney transplantation, especially in children with a long cumulative pre-transplant CPD duration. According to the ‘two-hit’ theory, EPS might occur when an initiating factor (second hit) is superimposed over a predisposing factor, such as peritoneal deterioration due to persistent injury caused by long-term CPD [24, 28]. The second hits may include acute episode of peritonitis and other acute intra-abdominal events, but also discontinuation of PD (including conversion to haemodialysis and transplantation). In post-transplant EPS, the exposure to calcineurin inhibitors has been suggested as a possible adjunctive risk factor. In fact, both tacrolimus and cyclosporine A have the ability to up-regulate transforming growth factor-β (TGF-β) expression, thus increasing the production of extracellular matrix [29].

Another aspect emerging from the results of our study was that we found a high incidence of EPS in children with FSGS. In our case series, FSGS was the primary renal disease in 5 out of 14 EPS patients (36%); altogether, the same chronic glomerulopathy was involved in 4 out of 16 paediatric EPS cases already published [4–7, 13]. It has been demonstrated that high glucose concentration induces an increase in TGF-β receptors type I and II in peritoneal mesothelial cells [30] and that the overexpression of TGF-β signal causes transdifferentiation of mesothelial cells (epithelial-to-mesenchymal transition) [31]. In the same way, a signal transduction cascade of the TGF-β/Smad signalling pathway, which is activated in the glomerular epithelial cells, appears to be involved in the development of either primary or genetic forms of FSGS [32, 33]. The existence of a common pathological mechanism in EPS and FSGS is an appealing concept, but prospective studies are needed to specifically analyse this association.

In our experience, the outcome of patients with EPS was worse than that of the total registry population. The mortality rate was high (43%), even 4-fold greater than that of our high-risk population of infants on CPD (9.5%) [1] and also greater than that reported by Hoshii et al. (27%) [4]. However, the Japanese case series did not include any post-transplantation EPS case that is more commonly associated with a severe outcome [28]. A limitation of our study was the lack of complete imaging, histology findings and treatment procedures in a few cases. However, this is the first among the existing paediatric case series to provide comprehensive information and one that can fairly characterize EPS in children.

In conclusion, this study provided the description of EPS in a large population of children who received CPD, showing that the incidence of EPS is associated with the duration of CPD also in paediatric patients. In long-term CPD patients, PD termination should be considered according to individual risk factors and early signs and symptoms of EPS. Moreover, the adoption of calcineurin inhibitors minimization immunosuppressive regimens should be considered in children on long-term CPD who underwent kidney transplantation [34]. Further studies are required to analyse the clinical correlation between FSGS and EPS occurrence on an even larger patient population, and to elucidate the physio-pathological relationship between these two entities.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES