Encapsulating peritoneal sclerosis: early diagnosis and risk factors
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CHAPTER 3

ENCAPSULATING PERITONEAL SCLEROSIS

State of Affairs

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INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) is the most severe complication of long-term peritoneal dialysis (PD). A fibrous cocoon covers the intestines and causes dysfunction leading to intestinal obstruction. The last decade more attention has been focused on this complication and several registries and study groups have been started \(^1,2\). Although this search has given us more insight into the pathophysiology and possible risk factors of the development of EPS, we still do not know how to prevent or recognize the development of EPS in the early stages. In the following review we will give an overview of the current status of EPS.

EPIDEMIOLOGY

The reported prevalence of EPS varies between 0.5- and 2.5\% \(^1-6\). The occurrence of EPS increases with the duration of PD therapy. A registry study from Australia described an incidence of 19.4\% after 8 years of PD treatment \(^5\). Kawanishi et al. confirmed this finding in a prospective study. The incidence of EPS increased with the duration of PD from 0.7\% after 5 years, 2.1\% after 8 years, 5.9\% after 10 years and 17.2\% after 15 years of PD therapy \(^6\).

The last years an overall increase of EPS incidence has been reported of 0.9\% in 1996 to 3.5\% in 2005 despite the overall decrease in PD population in some countries \(^2,3,5-8\). It seems unlikely that the increase in incidence is caused by over diagnosis or more attention for this complication. The clinical presentation of EPS is very severe and thus a missed diagnosis is implausible. Reported mortality rates of EPS are high, especially in the year of the diagnosis. Over the years mortality rates are between 25\% and 55\% and increase with the time on PD \(^2,3,5-8\).

EPS AND CLINICAL PRACTICE

Clinical presentation

Gandhi et al. were the first to describe EPS associated with intermittent PD, and the international society for peritoneal dialysis (ISPD) was the first to make a definition of this complication \(^9,10\). The ISPD stated that EPS is a clinical syndrome with signs of intermittent and persistent or recurring complaints of gastro-intestinal obstruction, with macroscopic and or radiological confirmation of sclerosis, calcification, peritoneal thickening or encapsulation of the intestines.

Even though this definition of EPS is not specific, the presence of a disturbed intestinal function such as the clinical symptoms of partial or total obstruction, are essential for the diagnosis. The first signs may be accompanied by increased parameters of inflammation. Nevertheless, at time of diagnosis of EPS, the obstruction often appears acute and non-infectious. In hindsight, abdominal complaints like nausea, complaints of changing defecation, and passage problems are often present in an earlier stage. The complaints may progress to severe abdominal pain, vomiting, anorexia, malnutrition, weight loss, and the development of an abdominal mass. The chronic and insidious nature of this developing clinical syndrome is specific for EPS \(^6\). As a consequence, EPS is often recognized in a late stage.

Blood-stained ascites may be present in the early stages of EPS; reports vary
between 7 and 50%. Peritoneal function often shows decreased net ultrafiltration (UF) and increased small solute transport. A laparotomy reveals several peritoneal alterations, such as a thickened, brownish peritoneum with several adhesions, and intestines that are partially or totally encapsulated in a thick fibrous tissue. In the last phase a complete or total sclerotic layer may cover the intestines, which gives it the appearance of a cocoon.

**Radiological diagnosis**

The diagnosis of EPS is often confirmed by different radiological measures. Abdominal ultrasound may demonstrate a thick walled mass containing bowel loops, loculated ascites and, fibrous adhesions at the time of EPS. Plain abdominal film may show gas fluid levels and dilation of the bowel lumen, indicating obstruction. In some patients, calcifications of the bowel wall are visible.

The CT scan is the most useful in confirming the clinical diagnosis of EPS. Peritoneal enhancement, peritoneal thickening, peritoneal calcifications, adhesions of bowel loops, signs of obstruction and fluid loculation/septation are visible at a CT scan at the time of EPS. The scan should be evaluated by a radiologist experienced in assessing scans of PD patients. The CT scan is not reliable for making an early diagnosis of EPS. Tarzi et al. studied 13 CT scans taken at least 4 months before the diagnosis of EPS. Only 3 out of 13 scans showed abnormalities, indicating that the CT scan cannot be used as a screening tool.

Two case reports on magnetic resonance imaging for the diagnosis EPS have been described. Dilatation of the intestines and circumscribed focal wall thickening, massive ascites with wall enhancement of the loculated ascites and compression of the bowel were found. In conclusion, all the above described radiological measures show signs of obstruction. The CT scan has been tested most frequently for the diagnosis EPS and appears to be the most reliable choice. Early diagnosis is not possible with radiological investigations.

**Therapy**

Surgical treatment of EPS is mostly performed in Japan. Kawanishi et al. showed that enterolysis is a successful alternative to the treatment of the abdominal cocoon. 96% of the patients reached restoration of abdominal transition. During this time consuming operation (on average 6.9h) the fibrosis and sclerosis is carefully peeled off the visceral and parietal peritoneum. Nowadays this operation is also conducted in Manchester. Because of the risk of reoccurrence, patients are treated with high dose of immunosuppressives immediately after operation.

The rationale behind immunosuppressive therapy in treatment of EPS is to treat the inflammatory state. Successful treatment of EPS with immunosuppressive therapy has been described with corticosteroids, azathioprine, mycophenolate mofetil (MMF) and sirolimus. Some of these reports are anecdotal and probably this is a biased view, because negative results are not likely to be reported. The positive effect of immunosuppressives appears to be in contrast with the observation of increased risk of EPS in the first year after transplantation, when patients are maximally immunocompromised.

Tamoxifen is a nonsteroidal anti-estrogenic drug that showed to be successful in several fibrosing diseases such as retroperitoneal fibrosis and sclerosing thyreoditis. Several small case-series have described positive effects of this drug on the treatment...
of EPS with improvement of the intestinal function and a decrease of the inflammatory features. A large English trial could not confirm this effect, perhaps due to the patient selection, as only 33% had the clinical symptoms of severe EPS. Adverse effects of tamoxifen in EPS patients, like thromboembolic events have been described by Eltoum et al. The risks of these events are probably outweighed by the devastating consequences of EPS.

Angiotensin II (ATII) inhibitors may be important in the prevention and treatment of EPS. ATII has proinflammatory and profibrotic effects which act through transforming growth factor-beta (TGF-β). The profibrotic features of ATII inhibitors have been shown in renal fibrosis. In vitro studies revealed that the production of TGF-beta induced by high glucose concentrations in human peritoneal mesothelial cells (HPMC) is inhibited by angiotensin converting enzymes inhibitors (ACEi) and angiotensin receptor blockers (ARB). Also in EPS models less fibrosis was found after ACE inhibition. In PD patients, ACE inhibitors appear to have a positive effect on the peritoneal function. We studied the duration of ACE therapy during PD in long-term PD patients who developed EPS and controls. There was no significant difference in the duration of ACEi/ARB exposure. However, only a small group was studied making it impossible to draw a firm conclusion.

**RISK FACTORS**

EPS is probably a multifactorial disease in which several risk factors must be considered. Many risk factors cause peritoneal changes and may play a role in the development of EPS. Even before the initiation of PD some alterations of the peritoneal membrane occur. Chronic renal failure induces some signs of vasculopathy and thickening of the submesothelial compact zone. The duration of PD is the most important risk factor for peritoneal alterations and EPS. This is probably because it represents the exposure to damaging influences, especially the exposure to dialysis fluids. PD fluids contain glucose which is a major cause of peritoneal membrane injury. Peritoneal specimens of PD patients showed that a high glucose load is associated with more submesothelial fibrous tissue. Patients with EPS had been exposed to more glucose compared to controls with similar PD duration. Furthermore, glucose forms glucose degradation products (GDP) during the heat sterilization process of PD fluids. GDPs accelerate the formation of advanced glycation end products (AGE).

New PD fluids contain less GDPs. Also, different dialysis solutions without glucose have been introduced such as icodextrin and aminoacids. Icodextrin has been studied most, especially since it caused episodes of culture negative peritonitis. This was due to contamination with proteoglycans. Recently, some studies have described an association between icodextrin use and serum markers of local inflammation such as, interleukin-6 (IL-6), tumor necrosis factor (TNF), and fibrin degradation products (FDP), but this was not found in others. A single dose of icodextrin proved to prevent adhesions after laparoscopic surgery in patients with a normal renal function. By and large, no convincing evidence is present that icodextrin causes structural alterations in peritoneal tissues.

Since the first reports on EPS, peritonitis episodes are considered risk factors for its development. In particular episodes caused by the Pseudomonas spp, Staphylococcus Aureus, Haemophilus Influenza or fungal peritonitis have been incriminated. The reports in literature on the importance of peritonitis in the
development of EPS remain equivocal. The Japanese prospective study showed that 25% of the EPS cases were associated with bacterial peritonitis while a single center controlled study showed no relationship. The recent Scottish registration and the Dutch multi center study could not confirm the association between peritonitis incidence and EPS. Nonetheless, the number of peritonitis episodes caused by Pseudomonas spp, Staphylococcus Aureus and fungal peritonitis was higher in the EPS group compared to controls. This indicates that not the incidence, but the cause of the peritonitis episode may be relevant for the development of EPS.

Chlorhexidine was used in the past to sterilize tubing connections. A strong association was found between the use of chlorhexidine and the development of EPS. In the early seventies an association between practolol and 3 cases of EPS have been described in patients without renal failure and without peritoneal dialysis. Other beta blockers have not been associated with EPS.

Observational studies showed that patients with EPS are often young. This common finding is difficult to interpret. It could represent a bias by indication since older patients are less likely to remain on PD for a long time and thereby have less exposure risk than young patients. It should be noted that young patients in general are the ones who have the best survival benefit of PD over hemodialysis, and only a small percentage develops EPS.

Another common finding in patients with EPS is dysfunction of the peritoneal membrane. EPS patients almost always have a fast transport status and ultrafiltration failure (UFF). The fast transport status reflects the effective peritoneal surface area which increased due to neoangiogenesis. This may cause a quick disappearance of the osmotic gradient and as a consequence ultrafiltration problems may develop. In a study by our group, patients with at least 2 years of PD treatment who developed UFF were studied. Half of the patients that developed this late UFF and continued PD therapy for 2 years or more, developed EPS. Therefore late UFF is considered a risk factor.

It is striking that most cases of EPS are diagnosed after the discontinuation of PD. In a prospective study 69% of the EPS cases occurred after the termination of PD therapy. The most common reasons to switch to hemodialysis therapy were recurrent peritonitis and UFF. Perhaps the cause of EPS after PD discontinuation is the lack of washing out and removal of fibrin, growth factors and cytokines. Subsequent studies with peritoneal lavage after the discontinuation of PD showed no effect in preventing EPS, except for one.

Some studies described a high incidence of post-transplantation EPS. In the Pan-Thames study the median time after transplantation until EPS was 5.4 months. A Dutch multi center study demonstrated that EPS usually develops in the first year after kidney transplantation. The yearly probability increased from 1.75% to 7.5%. The following years the probability decreased slowly. Different causes for this phenomenon have been proposed. The profibrotic properties of calcineurin inhibitors (CNIs) may be of influence on the development of EPS. Both cyclosporine and tacrolimus cause an upregulation of TGF-β and other fibrogenic genes in animal models. An experimental study showed that the administration of cyclosporine in rats chronically exposed to a 3.86% glucose based dialysis fluid led to peritoneal angiogenesis and fibrosis. Case-reports of EPS have been described in patients treated with tacrolimus after liver transplantation without chronic renal failure and without PD treatment. Furthermore, the introduction of CNI’s has also led to lower corticosteroid prescriptions after kidney transplantation. Corticosteroids may have a protective effect on the
development of EPS, and have been prescribed for treatment of EPS. It remains unclear whether post transplantation EPS is due to the discontinuation of PD or due to the transplantation itself. Figure 1 summarizes all these risk factors discussed above.

Figure 1 | A schematic representation of all the risk factors important for the development of EPS. All risk factors may lead to peritoneal changes and simple sclerosis and eventually EPS. However a minority of the PD patients undergo all stages.
PATHOPHYSIOLOGY

Alterations of the peritoneum

The peritoneum is built upon a monolayer of mesothelial cells and its basement membrane. Between the mesothelial layer and the vascular plexus lies the submesothelial compact zone with fibroblasts, macrophages and blood vessels. Several alterations of the peritoneum occur during the course of PD treatment. The mesothelial layer disappears (denudation). The peritoneal vasculature shows progressive signs of fibrosis and hyalinization of the media, due to the deposition of collagen IV (vasculopathy). New vessels develop (neoangiogenesis) and the more vessels develop, the more severe the interstitial fibrosis appears to be. The submesothelial compact zone thickening is caused by interstitial fibrosis and sclerosis that is composed of various types of collagen including collagen IV and myofibroblasts. Also advanced glycation end products (AGE) accumulate in the mesothelial layer, submesothelial layer and vascular wall with time on PD. The deposition of AGE is associated with the presence of peritoneal fibrosis and functional problems. It is unknown whether AGES cause peritoneal damage or are innocent bystanders. It is hypothesized that AGE accumulation influences the vessel wall and makes it more rigid, which would explain the association between AGE accumulation and fast solute transport.

Simple sclerosis is a mild sclerosis that may develop during PD. It is described as thickening of the parietal peritoneum and vascular alterations in absence of encapsulation. When bowel encapsulation is present, clinical signs of EPS become manifest. In EPS the parietal peritoneal specimens show fibrin deposition, fibroblast swelling, capillary angiogenesis, and mononuclear cell infiltration. Visceral peritoneal specimens show an excess of interstitial type IV collagen and a large number of peritoneal vessels. Whether EPS is the natural consequence of simple sclerosis, or whether they are two different disease entities remains a topic of debate. To study this, Garosi et al. compared the peritoneal thickness of peritoneal specimens of 224 patients that were treated with PD for 6 months to 12 years with peritoneal specimens of patients that developed EPS. Simple sclerosis was present in 180 of the 224 patients. In EPS group the visceral and parietal specimens were 10 to 50 times thicker compared to the control group. They concluded that there was no intermediate stage between simple sclerosis and EPS and therefore they are two different diseases. In contrast, a Japanese study compared peritoneal specimens of EPS patients and compared them to long-term PD patients. Angiogenesis, vasculopathy, new membrane formation, fibrosis and degenerative changes of the compact zone layers were present in both groups. Only the thickness of the compact zone and positive fibrin stains were unique for the EPS group. The peritoneal changes may gradually develop from peritoneal remodeling associated with long-term PD to simple sclerosis, and eventually EPS. However, no uniformity exists on this sequence, and not every patient progresses from simple sclerosis to EPS.
Pathogenetic factors at the cellular level

Growth factors, cytokines and enzymes

Several growth factors, cytokines and enzymes may be important for the development of fibrosis, neoangiogenesis and eventually EPS. Vascular endothelial growth factor (VEGF) plays an important role in the increased new vessel formation through proliferation and migration of endothelial cells. Several in vitro experiments have shown that HPMC have the capacity to produce VEGF in response to diverse stimuli present in PD fluids. An experimental model of EPS demonstrated the crucial role of VEGF in the development of neoangiogenesis, vasculopathy and thickening of the peritoneum in rats. This study showed a thinner compact zone and less vasculopathy in the EPS group treated with anti-VEGF compared to the EPS group not treated with anti-VEGF. This angiogenic inhibitory effect was confirmed in other studies.

VEGF has been demonstrated in peritoneal effluent, where it was locally produced or released by peritoneal tissues or cells. VEGF showed a linear relationship with the duration of PD treatment.

TGF-β appears essential in the formation of peritoneal fibrosis. TGF-β is important in different wound healing processes. Over expression of TGF-β is associated with several fibrosing syndromes. In vitro stimulation of HPMC with TGF-β leads to more collagen mRNA expression. The experimental model by Liu et al. demonstrated the role of TGF-β in the development of EPS in mice. This EPS model was developed using a helper-dependent adenovirus that actively transformed TGF-β. The short term exposure to the adenovirus expressing TGF-β led to simple sclerosis while longer exposure led to neoangiogenesis, extensive adhesions and coconuion or encapsulation of the intestines, also present in EPS. When tissue TGF-β binds to the TGF receptor different intracellular pathway signals are triggered. TGF-β signaling through SMAD seems to be a crucial element in the signal transduction pathways involved in wound healing and fibrosis. This was confirmed in an experimental study with SMAD3 knockout mice. These mice were resistant to peritoneal injury induced by TGF-β.

Other growth factors may also play a role in the development of peritoneal fibrosis. A positive correlation has been reported between the thickness of the peritoneal membrane and the expression of mRNA connective tissue growth factor (CTGF). Effluent CTGF levels correlated with dialysate-over-plasma ratios of creatinine and the estimated local peritoneal production of CTGF. An association between CTGF and fibrosis has not been demonstrated and needs to be studied. Fibroblast growth factor (FGF) participates in several fibrotic diseases and induces the proliferation of various cultured cells such as fibroblasts and endothelial cells. In vitro study of mesothelial cells exposed to a high glucose concentration showed more mRNA expression of FGF. FGF has not been demonstrated in clinical PD studies. Therefore it is unknown whether FGF is involved in EPS. Platelet derived growth factor (PDGF) is involved in many wound healing processes. Daily addition of PDGF to cultured cells stimulated collagen production. The effect of PDGF expression on angiogenic and fibrotic effects in the mice peritoneum has also been studied. An adenovirus mediated gene transfer was used. The over expression of PDGF led to a normal wound healing response with angiogenesis and fibroblast proliferation. However it did not lead to collagen protein expression. It can be concluded that PDGF is not responsible for the peritoneal membrane injury.

AGE accumulates in the peritoneal structures with time on PD. In vitro AGES induce collagen and TGF-β expression in human peritoneal mesangial cells.
Experimental studies showed that ligand binding of AGE to its receptor (RAGE) led to submesothelial fibrosis, interstitial collagen and fibronectin accumulation. The peritoneal expression of RAGE is increased in settings of diabetes and uremia. Plasminogen activator inhibitor 1 (PAI1) and tissue-type plasminogen activator (tPA) are involved in fibrogenesis of various organs and can be produced by mesothelial cells. An in vitro study showed that HPMC produce PAI1 and t-PA in response to glucose based PD solutions. A mouse model of peritoneal fibrosis showed that tPA aggravates peritoneal fibrosis, neoangiogenesis and peritoneal inflammation. It remains unclear whether plasminogen is involved in the development of EPS.

In addition to increased formation of fibrosis a decreased degradation of fibrous tissue also contributes to the accumulation of fibrosis in the peritoneum. Metalloproteases (MMP) are enzymes important in tissue destruction and excessive remodeling. The gelatinases (MMP2, MMP9) help degrading the extracellular matrix such as collagen IV and fibronectin. Experimental EPS studies showed increased MMP2 levels in effluent, and inhibition of MMP2 led to less peritoneal injury. A multicenter study investigated the MMP2 and MMP9 levels in effluent of EPS patients and PD patients with peritoneal injury. Patients with infectious peritonitis had high MMP9 levels. PD patients with mild peritoneal injury (ascites<100mL) had the highest MMP2 levels. EPS patients had moderate high levels of MMP2. However, half of the patients with MMP2>600ng/mL ended up with EPS (7 out of 15). An in vitro study of HPMC exposed to glucose demonstrated that a decreased expression of MMP1, 8, 13 and an increased expression of tissue inhibitor metalloproteinase (TIMP) leads to ECM accumulation. Whether MMP play a role in the development of EPS is uncertain. Mast cells produce tryptase, which has a fibrinolytic function. In an inflammatory state an increased number of mast cells is present in the peritoneum. Also in PD patients without any complications an increase of mast cells is found. However a recent histochemical study demonstrated that the number of mast cells in the peritoneum of EPS patients is extremely low, comparable to patients without inflammation.

Tumor necrosis factor-alpha (TNF-alpha) stimulates in vitro macrophages to induce neoangiogenesis and fibroblast proliferation. Zemel et al. measured TNF-alpha in effluent and demonstrated that it was only produced by peritoneal tissues or cells in case of peritonitis. A role of TNF-alpha in the development and early diagnosis of EPS is unclear. A scheme of potentially relevant factors in the development of EPS is given in Table 1.

Epithelial to mesenchymal transition

Epithelial to mesenchymal transition (EMT) is a physiological process which occurs throughout the body and in the peritoneum to repair damaged tissue. During EMT, mesothelial cells that have been exposed to dialysate undergo a morphological and functional alteration that changes their epithelial phenotype to become fibroblast. These fibroblasts then migrate to the submesothelial compact zone and may overproduce TGF-β. This process starts at the initiation of PD treatment and continues with the duration of PD. EMT is necessary for tissue repair under normal conditions, but uncontrolled it may lead to fibrotic processes. Characteristics of EMT were present in fibrotic tissue, predominantly in the submesothelial layer.

TGF-β plays a central role in EMT. The addition of TGF-β to HPMC leads to a myofibroblastic conversion of these cells. An experimental model demonstrated that TGF-β is a promoter of EMT. Although TGF-β signaling through the SMAD pathway seems crucial in the processes of wound healing and fibrosis, the role of
SMAD in EMT remains controversial\textsuperscript{139-141}.

Several growth factors and cytokines important for the development of fibrosis, are produced by mesothelial cells that have undergone EMT. An ex vivo experiment showed higher VEGF production in mesothelial cells with fibroblastic features compared to mesothelial cells with an epithelial phenotype\textsuperscript{142}. A Japanese study showed that MMP2 was produced by myofibroblast-like mesenchymal cells\textsuperscript{130}. The binding of AGE to its receptor may result in EMT of the mesothelial cell with peritoneal fibrosis\textsuperscript{143}. Other important promoters of EMT and the subsequent peritoneal fibrosis are MMP2, IL-1, transcription factor SNAIL\textsuperscript{135,144}.

Many interventions have been tested in animal models. EMT may be reversible in the early stages. Perhaps the loss of mesothelial cells can be regenerated\textsuperscript{145}. Also the transition of mesothelial cells may be influenced for instance by hepatocyte growth factor (HGF) which may be able to block and reverse EMT\textsuperscript{136,146,147}. In a recent study EMT was detected in parietal peritoneum of early PD patients (up to 2 years). EMT was defined as the presence of cytokeratin and alpha-smooth muscle actin in the specimen. In this study an association was suggested between fibrosis through EMT

<table>
<thead>
<tr>
<th>Relevant factors for the development of EPS at cellular level</th>
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<td>VEGF</td>
<td>In vitro</td>
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<td>In humans</td>
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<td>TGF-beta</td>
<td>In vitro</td>
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<td>SMAD</td>
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<td>CTGF</td>
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<td>FGF</td>
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<td>PDGF</td>
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<td>AGE</td>
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<td>PAI1</td>
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<td>MMP</td>
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<td>Mast cells</td>
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<td>TNF</td>
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<td>EMT – in vitro</td>
<td>TGF-beta</td>
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<td>HGF</td>
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and a fast transport status without an increased vascular surface area. Fibrosis and fast transport status are associated with EPS. Although EMT is generally being accepted, the contribution of EMT to the processes of EPS remains unclear.

THEORIES ON THE PATHOGENESIS OF EPS

Two hit theory
The “two-hit theory” of EPS hypothesizes that 2 factors are required for the onset of EPS. The first hit causes disruption of normal peritoneal and mesothelial physiology. This disruption generally occurs over a period of years and is a consequence of PD treatment. EMT takes care of the physiological repair process. During this time the patient may be predisposed to a second hit that triggers the development of EPS. The second hit may be a peritonitis episode, the discontinuation of PD treatment or perhaps a genetical predisposition. The second hit theory was first described by Kawanishi et al. and is now generally accepted.

Genetic predisposition
Most patients that start PD treatment will never develop EPS. A genetic predisposition may influence the development of EPS. Several polymorphisms of important factors in the development of EPS are known such as TGF-β and VEGF. To study the genetic association with EPS a large DNA database has been started in Great Britain.

We have described the joint occurrence of EPS and Alport syndrome. Since both diseases are rare, the combined presence would seem highly unlikely. Yet in our center, 2 out of 13 EPS patients had Alport syndrome as a primary kidney disease. Perhaps Alport syndrome predisposes the development of EPS. Alport syndrome patients miss collagen IV in their basement membranes. In the skin collagen IV is replaced by collagen VII. This collagen is often found in scar tissue. It is unknown whether this replacement of collagen IV by collagen VII in the skin also occurs in the peritoneum.

EARLY DIAGNOSIS

Making an early diagnosis of EPS could prevent the severe onset of this condition by starting therapy in an earlier stage. Between the stage of normal PD and EPS there must be a stage of pre-EPS. As mentioned previously, no radiological screening tools are available for early diagnosing EPS. Up to now pre-EPS is ill defined, the number of patients that progress to the pre-EPS stage and do not develop EPS is unknown. Several attempts have been made to stage EPS, for instance Nakamoto who divided the development of EPS in 4 clinical stages: a pre-EPS period, an inflammatory period, encapsulating or progressive period and, complete bowel obstruction/cocoon. Functional characteristic features of a pre-EPS stage are UFF and fast solute transport. Several diagnostic investigations for an early diagnosis have been studied; they will be discussed in the following paragraphs.
Functional parameters of the peritoneum

The morphological changes of the peritoneum may influence peritoneal function. Up to date investigations of EPS and peritoneal function have been scarce. Verger et al. was one of the first to describe the decrease in ultrafiltration and hyperpermeability in a patient with EPS. Since then other studies have found similar results. However, these features are not specific for the development of EPS. In a recent study a number of peritoneal function parameters was followed in the 4 years prior to the diagnosis EPS. Small solute transport increased until two year prior to the diagnosis of EPS and then decreased again. Water transport decreased in the four years prior to EPS. In a sequel of this study we compared the time courses of peritoneal transport parameters of EPS patients to long-term PD patients with and without UFF. UFF was defined as net UF<400mL/4h/3.86%. EPS and UFF patients had similar time courses. Additionally we studied all patients that developed UFF after at least 2 years of PD. In our PD population half of the patients that continued PD for 2 years or more after late UFF was determined, developed EPS. The combination an initial increase followed by a decrease in small solute transport, a declining free water transport, and UFF may indicate limited intrinsic transport through the interstitium in EPS, possibly due to interstitial fibrosis. In order to determine a fast transport state and UFF the peritoneal function should be assessed annually basis with a 3.86% glucose test.

Effluent Markers

Several substances in PD effluent may serve as a surrogate marker for structural and functional alterations of the peritoneum. Some of these substances have been studied specifically for the diagnose EPS. Cancer antigen 125 (CA125) is a marker for mesothelial cell mass. In the years prior to the diagnosis EPS CA125 values were extremely low, which could represent the denudation of mesothelial mass. IL-6 is a marker for inflammation and 2 years prior to the diagnosis EPS values were very high. The combined appearance rates of CA125 and IL-6 had a sensitivity of 70% and a specificity of 100% for the diagnose of EPS in patients with UFF. This makes them potentially useful for an early diagnosis of EPS.

All growth factors and cytokines involved in the process of peritoneal fibrosis and neoangiogenesis are potential (early) diagnostic markers for EPS. However, few studies investigated effluent markers. Possible candidates are discussed in the following paragraph. TGF-β appears important in the development of EPS. An inactive form of TGF-β has been demonstrated in peritoneal effluent, but the active form is not soluble. Besides, soluble TGF-β is difficult to analyze in plasma or effluent because the circulating form binds to alpha-2-macroglobulin, and is therefore not useful in the diagnosis of EPS. Hyaluronan is an important substance in the extracellular matrix. Hyaluronan measured in effluent increases with the duration of PD and in patients with UFF. However it was not increased in patients with peritoneal adhesions. Whether hyaluronan is an early diagnostic marker still needs to be studied. Fibrin degradation products in effluent correlated with dialysate-to-plasma ratios of creatinine. Fibrin degradation levels in effluent were high in 16 patients, 1 of which developed EPS. The value of this substance as a marker for EPS needs to tested in a different PD population. Hydroxyproline in tissue is a gold standard for the assessment of fibrosis. However, in an experimental study hydroxyproline measured in peritoneal effluent was not locally produced and thus not useful as a marker for peritoneal fibrosis. Effluent MMP2 has been studied as a diagnostic marker and seemed to correlate with profibrotic events.
WHAT A NEPHROLOGIST SHOULD KNOW ABOUT EPS

The increased attention for EPS has led to more insight in the pathophysiology of this complication. It has an impressive time course. Although the prevalence of EPS may have increased, it remains a rare disease and contributes only marginally to over-all mortality of PD patients. This confirms the contention that PD is a good alternative for hemodialysis.

A scheme linking the various proposed stages of EPS to pathological and clinical findings is given in Table 2. The diagnosis of EPS is made on the presence of bowel obstruction and a CT scan. Identifying EPS in an early stage is difficult. Net UF below 400mL/4h/3.86% and the appearance rates in effluent of CA-125 below 33mL/min and IL-6 above 350mL/min may be specific for the development of EPS. Patients that develop a net UF below 400mL/4h/3.86% should discontinue PD therapy within 2 years. Therefore the peritoneal function should be measured annually with 3.86% glucose dwell for 4 hours and effluent samples should be taken.

Patients have an increased risk of developing EPS when PD is discontinued, especially when UFF is present. The decision of switching patients to hemodialysis should take into account the high possibility of infection, the hemodynamic instability and different quality of life. There are no data on the prospective change of PD to HD. However an ISPD study group concluded that changing PD to HD in order to prevent the development of EPS is unnecessary. When EPS is suspected treatment with corticosteroids or tamoxifen should be considered.

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<tr>
<th>Stage</th>
<th>Pathological findings</th>
<th>Clinical symptoms and investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-EPS/Asymptomatic period</td>
<td>Mesothelial denudation, Vasculopathy, Peritoneal thickening due to fibrosis, Peritoneal calcifications</td>
<td>Ultrafiltration failure, Fast transport status, Ascites</td>
</tr>
<tr>
<td>Inflammation period</td>
<td>Inflammation, mononuclear cells, Fibrin degradation products</td>
<td>Loss of appetite, weight loss, diarrhea and changes in defecation. Fever. Blood-stained ascites. Increase in CRP levels, leukocytes.</td>
</tr>
<tr>
<td>Progressive or &quot;encapsulation&quot; period</td>
<td>Inflammation decrease, Adhesions and progressive encapsulation</td>
<td>Disappearance of the signs of inflammation Gastro-intestinal obstruction:  • Nausea, vomiting  • Abdominal complaints, obstipation  • Ascites, abdominal mass  • Blood stained effluent</td>
</tr>
<tr>
<td>Complete bowel obstruction/ cocoon</td>
<td>No inflammation</td>
<td>Anorexia and complete ileus Abdominal mass</td>
</tr>
</tbody>
</table>
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