Encapsulating Peritoneal Sclerosis: Clinical Significance and Implications

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Abstract
Encapsulating peritoneal sclerosis (EPS) is a rare but serious complication of peritoneal dialysis (PD). This review discusses the current understanding of the aetiology and pathogenesis of EPS, highlighting histological features which differentiate it from simple sclerosis of the peritoneal membrane which develops with time on PD. Diagnostic criteria are presented, including the role of imaging techniques. To date there are no randomised controlled trials to guide therapy; however, surgical techniques are an important treatment option. Collaborative research will be essential if this serious problem facing PD is to be solved.

Introduction
Encapsulating peritoneal sclerosis (EPS) is a rare but potentially devastating complication of peritoneal dialysis (PD). Diagnosis comprises the fulfilment of two key criteria: firstly, symptoms that might indicate an obstructive ileus, which may range from mild symptoms such as anorexia to marked weight loss and bowel obstruction [1], and secondly the demonstration, either at laparotomy or from imaging techniques, that this ileus is due to peritoneal membrane thickening resulting in encapsulation and cocooning of the bowel. However, it is recognised that onset is often insidious, presenting with non-specific features of inflammation, weight loss and abdominal discomfort, whereas the full-blown form can cause failure of the gastrointestinal tract and death. Its sporadic nature, the difficulty in early diagnosis, as well as the lack of suitable animal models, means that at present the understanding of risk factors of EPS is incomplete and evidence-based therapies are lacking. In some patients, EPS seems to be a self-limiting condition that can be managed with appropriate nutritional support, whereas in others the progression is rapid with the development of obstructive features, and in these cases there is growing evidence that timely surgical intervention can be successful.

Aetiology
The incidence of EPS varies between reports partly as a consequence of difficulties with diagnostic definition requiring sufficient sensitivity to include all cases while...
maintaining specificity. In a prospective study from Japan, the incidence rates and mortality rates increased with time on PD ranging from 0% at 3 years to 5.8% at 10 years to 17.2% with 100% mortality in patients on PD for over 15 years [1]. EPS is not exclusive to PD and has been associated with a range of conditions, including systemic autoimmune disease, diseases of the gastrointestinal tract, peritoneal and intra-abdominal malignancies, exposure to talc or particulate matter or the use of intraperitoneal disinfectant for peritoneal lavage and β-blocker administration [1]. Although peritoneal sclerosis can be induced in animal models by infusing a range of sclerosant agents into the peritoneal cavity [2] and more recently the introduction of profibrotic agents delivered to the peritoneum via adenoviruses [3], it has been difficult in animals to adequately mimic the human condition where prolonged dialysis in the context of uraemia and inflammation contributes to the formation of the abdominal cocoon. In PD patients, clinical associations have been identified with acetate buffer [4], chlorhexidine, severe PD peritonitis (in particular when due to *Staphylococcus aureus, Pseudomonas, Enterococcus*), dialysate glucose exposure [5], low ultrafiltration capacity [6], absence of residual renal function (at least in children) [7] and time on PD as well as, rather paradoxically, discontinuing it [1]. The latter risk factor possibly explains recent reports of an increase in EPS following renal transplantation [8].

**Pathology and Pathogenesis**

A ‘two-hit’ hypothesis for EPS has been proposed in which disruption of normal peritoneal/mesothelial physiology as a consequence of exposure to PD that occurs generally over a period of years predisposes the individual to a second hit that triggers the process [9]. This second hit may take the form of an episode of peritonitis, discontinuing PD, or an acute intra-abdominal event.

Peritoneal membrane thickening and sclerosis occur commonly in patients on PD [10]; however, it is not clear whether simple sclerosis and EPS represent distinct pathological entities or a spectrum of severity of the same disease process [11]. The principal histological feature of simple sclerosis is increased peritoneal membrane thickness, which is already present in uraemic patients at the start of dialysis [12], increases progressively with time on PD, is more prominent in patients with impaired ultrafiltration capacity and is associated with reduction in arteriolar and venular lumen/vessel diameter ratio. On the other hand, histological study of EPS tissue demonstrates mesothelial denudation and capillary angiogenesis as well as interstitial fibrosis and vascular sclerosis. Additional features include inflammation and fibrin deposition, predominantly affecting the visceral membrane [9]. Others have confirmed fibrin deposition, but did not find that the degree of angiogenesis, vasculopathy, new membrane formation or fibrosis was different between EPS and cases of simple sclerosis [13].

A pathogenetic schema links plasma exudation and fibrin deposition with adhesion and fibrosis (fig. 1). Fibrinous exudation, as a response to peritoneal membrane inflammation, may result in adherence of membrane surfaces and can either be absorbed or invaded by fibroblasts to become a permanent adhesion. Loss of normal mesothelial physiological responses, including production of fibrinolytic agents, increases the likelihood of the formation of a fibrinous adhesion. There is evidence that patients susceptible to adhesion following gynaecological

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**Fig. 1.** A diagram of the possible pathogenetic mechanisms in the development of EPS. EMT = epithelial mesenchymal transformation; GDP = glucose degradation product; IL-6 = interleukin-6; MMP = matrix metalloproteinase; PAI-1 = plasminogen activator inhibitor type 1; TGF = transforming growth factor; VEGF = vascular endothelial growth factor.
surgery exhibit local fibrinolytic abnormalities. Plasmin has a central role not only in fibrin degeneration, but also in the breakdown of extracellular matrix, activation of metalloproteinases, and activation of uPlasminogen activator – and thus may be central to the process [14]. An overexpression of TGF-β1 is associated with adhesion formation, possibly through a mechanism involving local regulation of plasminogen activator inhibitor type 1 [15].

The molecular mechanisms involved in the development of EPS are complex and include dysregulation of growth factors combined with subclinical bowel ischaemia resulting in transmigration of gut organisms across the bowel wall.

In parallel with fibrosis, the peritoneum shows a progressive increase in capillary number (angiogenesis) and vasculopathy, resulting in increased solute transport across the peritoneal membrane and ultrafiltration failure. Glucose and glucose degradation products contained in the dialysate may have a role in peritoneal deterioration and stimulate transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF) production by mesothelial cells. TGF-β is a potent profibrotic factor and induces epithelial-mesenchymal transition of the mesothelial cells. Local production of VEGF during PD plays a central role leading to peritoneal neoangiogenesis and PD functional decline [16].

**Diagnosis**

Clinically, the diagnosis of EPS is based on the finding of abnormalities in gastrointestinal function [1]. Symptoms include early satiety, anorexia, nausea, vomiting, constipation, diarrhea, weight loss, abdominal fullness and pain [17]. Signs of inflammation may be pyrexia, raised CRP, anaemia, bloody dialysate, and ascites. Abdominal masses and pain may indicate peritoneal adhesions and/or coocooning, and there may be features of acute or subacute intestinal obstruction. Loss of peritoneal ultrafiltration capacity is common and a rapid increase in small solute peritoneal transport as defined in the peritoneal equilibration test has also been described. The differential diagnosis includes TB peritonitis, peritoneal mesothelioma, carcinomatosis or posttransplant small bowel lymphoma, and it is important to obtain histology where there is doubt. Japanese investigators [17] have subcategorised EPS into four stages: pre-EPS; an inflammatory stage; an encapsulating stage, and finally a stage of bowel obstruction. Classifying the diagnosis according to progressive stages has the potential for therapeutic strategies to be appropriately targeted to the phases of development.

Current imaging techniques are insufficiently sensitive to detect the early stages of EPS. Screening with CT is of limited value since up to 50% of patients with established EPS have had a normal abdominal CT within 2 years prior to diagnosis [18], whereas peritoneal abnormalities are present in approximately 7% of patients on long-term PD who do not develop EPS, with thickening and enhancement being most prevalent [19]. CT scanning is the investigation of choice in patients with established EPS [19, 20] (table 1; fig. 2) and is useful for monitoring disease progression. However, interpretation can be difficult and scans should be read by an experienced radiologist familiar with the condition. Findings include peritoneal enhancement after intravenous contrast, which is usually associated with peritoneal thickening,
although these appearances are not specific to EPS and are also seen in peritoneal carcinomatosis, tuberculosis and pseudomyxoma peritonei. Peritoneal calcification is mainly found in established cases and may manifest as a small focal area, fine linear pattern or extensive conglomerate calcification. The most specific features on CT are bowel tethering and peritoneal calcification [18]. Bowel tethering is caused by fibrosis in the root of the mesentery in addition to previsceral membrane formation and is most easily assessed if the bowel lies within a loculated fluid collection (cocoon). Other CT features include bowel wall thickening and dilatation which may be associated with obstruction. Ultrasound findings include increased peristalsis, bowel tethering, ascites and visualisation of a previsceral membrane [21]. The main feature on barium studies is delayed transit [22], but there may also be an abrupt change in calibre where normal bowel joins with an encapsulated segment, separation of rigid bowel loops and disordered peristalsis [23]. MRI is not particularly helpful since it is not good at assessing peritoneal calcification and there are concerns about nephrogenic systemic fibrosis from contrast studies in dialysis patients.

Management

There are no randomised controlled trials to inform the management of patients with EPS and the level of evidence is weak. Reported therapy includes the use of immunosuppressant agents, predominantly corticosteroids, the antifibrotic agent tamoxifen, nutritional support and surgery to remove the fibrotic material (enterolysis/adhesiolysis) [24]. In a registry report from Japan, out of a total of 1,958 patients treated with PD, 48 developed EPS in whom the recovery ratio with total parenteral nutrition, corticosteroids and surgical treatment were 0, 38.5, and 58.3%, respectively [25]. Nutritional assessment and support is critical to patient outcome, and patients may require enteral or parenteral support, with preoperative optimisation of patients undergoing enterolysis being essential [26]. Surgery has an important role in the management of established EPS and is probably currently the only definitive therapeutic measure. Kawanishi et al. [27] reported that enterolysis was successful in 81 of 86 cases with, however, a 23% recurrence rate. In the UK, the Manchester group has carried out peritonectomy and enterolysis in 62 cases of established EPS since January 2000. 43 (69%) patients are currently alive and well. Mortality in this series has been mainly in the advanced cases operated on as surgical emergencies [publication in preparation].

There is an urgent need to precisely define the role and timing of surgery in EPS. Currently described poor outcomes of surgery in individual cases or small case series are a consequence of delayed surgical intervention, often as an emergency in nutritionally depleted, septic and obstructed renal failure patients. It highlights the need to have well-defined criteria for diagnosis, length of medical treatment with timely recognition of failure of medical treatment and referral for surgery before the patient’s condition deteriorates. Furthermore, it is critical that the patient’s condition is optimised prior to surgery. Good surgical outcomes require a multidisciplinary team, with surgeons experienced in peritonectomy and enterolysis, along with intensive perioperative haemodilysis, parenteral nutrition, physiotherapy and critical care. Operative management entails stripping of the thickened parietal and visceral peritoneal membrane (peritonectomy) and release of the small bowel obstruction (enterolysis) and can last several hours, be demanding and require the utmost care to avoid an inadvertent enterotomy, which could be a fatal complication. Providing surgical care for EPS patients has significant implications for service development and training to ensure sufficient expertise in this area. In the UK, the National Specialist Commissioning Group has designated Manchester and Cambridge as national referral centres for the surgical treatment of established cases of EPS from April 2009. With centralising and increasing experience at these two centres already undertaking peritonectomy and enterolysis, it is envisaged that overall outcomes can be further improved while facilitating further research into EPS.

Table 2. Recommendations for clinical practice

1 CT scanning is a valuable technique for monitoring patients with a diagnosis of EPS, but is insufficiently sensitive to be used for screening purposes.

2 Patients in whom a diagnosis of EPS is made should have an early assessment by a surgeon with particular experience in the management of EPS. This is particularly important if there are features to indicate incipient bowel obstruction.

3 In PD patients who are beginning to develop ultrafiltration difficulties that are not amenable to the use of modest dialysate glucose concentrations and icodextrin, consideration should be given for a planned transfer to haemodialysis.
Prevention

An understanding of the aetioloogy of EPS should lead to a reduction in the risk for patients on PD [28]. Thus, low glucose exposure, preserved residual renal function, little or no peritoneal infection, and low small solute transport status may confer a lower individual risk. PD management should focus on minimising glucose exposure and peritonitis rates. Japanese data has suggested a dramatic increase in the incidence of EPS after 8 years on therapy and recommendations have been made to pre-emptively discontinue PD at that stage [24]. The dilemma is that for some patients, discontinuation is a risk factor for triggering EPS.

References


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The Way Forward – The Need for an International Registry

It is clear that there is much to do to improve our understanding of EPS, and this will require a collaborative research approach. In the UK, an EPS registry and DNA bank have been established in the context of a nationwide PD research network with support from the International Society of Peritoneal Dialysis (ISPD) and the Kenyon Gilson Fund [29]. Objectives include the development of a risk-based approach to clinical decision making by collating detailed risk factor data in combination with genetic analysis and additional biomarkers and correlating these with outcomes. Candidate genes include genes of fibrosis (TGF), angiogenesis (VEGF, RAGE), and inflammation (TNF, IL-6). Such a research network will also permit better understanding of the effects of treatment and indeed provide a platform for clinical trials and will necessarily collaborate internationally. It is hoped that through such an initiative, EPS will cease to haunt PD in the foreseeable future.
This review addresses an important, serious and often underestimated complication of long-term CAPD, namely encapsulating peritoneal sclerosis (EPS). Augustine and colleagues have highlighted in their review the clinical, pathological as well as radiological features of EPS. They also review the pathophysiology of the peritoneal fibrosis which shares common pathways with other forms of fibrosis, including a putative important role attributed to transforming growth factor-β1. The authors examine critically the limited available data on surgical and medical interventions. They draw some conclusions and a list of recommendations and guidelines for early detection and management. They also draw attention to the recently formed UK EPS registry and DNA bank to foster clinical collaboration and research in the field. This registry is supported by the International Society of Peritoneal Dialysis (ISPD) and the Kenyon Gilson Fund. Readers with an interest in the field should contact Dr. Martin Wilkie at the Sheffield Kidney Institute, Sheffield, UK (martin.wilkie@sth.nhs.uk).