The aim of this paper is to provide an overview of EPS and relate it to clinical practice.

- To help health care professionals (HCPs) understand the pathophysiology of EPS
- To identify early signs and symptoms and patients at risk
- To examine the clinical features of EPS
- To guide HCPs when it is appropriate to refer patients to a specialist centre for interventions.

Introduction

EPS is a rare but serious complication of peritoneal dialysis (PD) and can be fatal. In the last ten years there have been several publications on incidence and research in the field of EPS, yet many aspects of EPS are still not fully understood. Various terms have previously been used for the condition, but encapsulating peritoneal sclerosis best describes the morphological process, in which acute inflammation or peritonitis may be absent during later stages of the condition.1

Patients diagnosed with EPS face a potentially life threatening condition and the prospect of major surgery, with often prolonged periods in hospital and lengthy recovery time. This can affect their quality of life and cause immense distress to them, their families and carers. With increased awareness and continued research the patient experience can only be enhanced as HCPs endeavour to provide better treatments to patients. The rarity of the condition however makes this task difficult.

Diagnosis

The diagnosis of EPS remains a contentious issue as gold standard criteria cannot be simply applied. Patients who experience EPS may have had symptoms for several months, in many cases undetected. The criteria initially recommended by the International Society of Peritoneal Dialysis (ISPD) have been updated to include four stages to EPS 2. An ISPD position paper also describes the diagnostic criteria 3. Another review suggests a structure for reporting EPS and includes histological and macroscopic appearances 4. Table one combines these reports but does not include all the features.

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Features</th>
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<tbody>
<tr>
<td>Clinical Features and Symptoms</td>
<td>Gastrointestinal:</td>
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<tr>
<td></td>
<td>• Initially mild, occasional nausea, vomiting, indigestion</td>
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<tr>
<td></td>
<td>• Progressively worsening, anorexia, weight loss, pain, vomiting and alteration of bowel habitus</td>
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<tr>
<td></td>
<td>• Obstructive symptoms then occur requiring intervention</td>
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<td></td>
<td>Inflammatory:</td>
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<tr>
<td></td>
<td>• Raised CRP, hypoalbuminaemia</td>
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<td></td>
<td>• Prolonged sterile peritonitis</td>
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<td></td>
<td>Membrane Function/PD:</td>
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<tr>
<td></td>
<td>• Change in peritoneal transport status</td>
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<tr>
<td></td>
<td>• Ultra filtration failure</td>
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<tr>
<td></td>
<td>Haemoperitoneum</td>
</tr>
<tr>
<td>Radiological Features</td>
<td>Computerised tomography (CT) will only show evidence of later stages but include:</td>
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<tr>
<td></td>
<td>• Peritoneal calcification</td>
</tr>
<tr>
<td></td>
<td>• Bowel thickening</td>
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<tr>
<td></td>
<td>• Bowel tethering</td>
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<tr>
<td></td>
<td>• Bowel dilatationLoculation</td>
</tr>
<tr>
<td>Surgical Features</td>
<td>Sclerosis or tanning of small bowel</td>
</tr>
<tr>
<td></td>
<td>Encapsulation</td>
</tr>
<tr>
<td></td>
<td>Calcification</td>
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<tr>
<td>Macroscopic</td>
<td>Sticky fibrin coating the peritoneal membrane</td>
</tr>
<tr>
<td></td>
<td>Classical cocooning with a sclerotic capsule</td>
</tr>
<tr>
<td>Histological</td>
<td>Not yet described well in detail to be used as specific for diagnosis but includes:</td>
</tr>
<tr>
<td></td>
<td>• Vasculopathy</td>
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<tr>
<td></td>
<td>• Acute inflammation</td>
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<td></td>
<td>• Chronic inflammation</td>
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The initial suspicion usually arises from signs of bowel obstruction and features of encapsulation. Earlier indications of malnutrition, weight loss, abdominal distension, bowel disturbances and vomiting are all common. When obstruction occurs it usually points to EPS and can be confirmed by computed tomography (CT) or laparotomy. It has recently been recommended to use a scoring system for CTs especially when reporting EPS cases for research. One of the key distinguishing features of EPS is the intermittent nature of the clinical syndrome as other causes would be more acute or have permanent manifestations.

Pathophysiology

The process of fibrosis which takes place in EPS can happen with all patients receiving PD, but the development of an additional adhesion process is believed to occur in EPS. A number of hypotheses have been advanced relating to injury to the peritoneum, including genetic predisposition. The theory put forward described as a “second hit” relates to the fact that all patients exposed to PD will have disruption to normal peritoneal mesothelial structure and physiology, but a second hit which maybe acute peritonitis, discontinuing PD or an acute intra-abdominal event then precipitates EPS. Research continues to examine the processes of fibrosis to try and identify markers from laboratory based tests for fibrotic damage and/or possible early indicators of EPS. Some of this work in proteomics and metabolomics is in progress.

Risk Factors and Incidence

Several larger studies have aimed to identify risk factors of EPS and the most recognised risk is the length of time on peritoneal dialysis. Other risks have been identified such as the use of hypertonic glucose dialysate and more so membrane failure. On the other hand, a significant proportion of cases of EPS develop after PD has been discontinued following transfer to haemodialysis (HD), or after renal transplantation. However there is no current evidence that stopping PD is the cause of EPS, in fact some studies indicate that it was likely that early signs of EPS were present before the switch to HD.

The questions that remain unanswered are does stopping PD cause EPS or was EPS already developing and so does stopping PD expedite the EPS process? Studies now being developed may provide some answers in particular a prospective long-term follow-up of PD patients and outcomes.

Incidence of EPS has been reported from across the world and overall incidence is relatively low at 3.3% in a UK cohort. Evidence of increased risk with time on PD has also been published; i.e Japan 0% at three years, 5.8% at ten years and 17.2% at 15 years with 100% mortality. Overall incidence from the Scottish Registry is 2.8% but 8.1% after eight years. There are also some discrepancies and differences of reported incidence at two and three years on PD. Often these differences are due to variable case mix, diagnostic criteria and methodology used. In one report from Australia and New Zealand all the cases were diagnosed while undergoing PD, but the paper does not state the criteria used for diagnosis. Some studies demonstrate a greater incidence of EPS in younger patients. There is speculation that increased exposure to large dialysate volumes, as seen in APD and icodextrin solutions, may also be a risk factor.

However, it is difficult to draw conclusions from these studies because it is known that in membrane failure (ultrafiltration failure) larger volumes, with greater glucose and icodextrin exposure, are used. The primary risk is therefore membrane failure rather than exposure to these higher concentrations. There are also concerns of EPS following transplantation as more reports are published and some hypothesis of a different pathogenic process.

The consensus is that up to two years the risk of EPS is less than 1%, but the risk increases thereafter with time on PD, in particular after four years when the risk increases with each subsequent year on PD therapy. There is an increased awareness of EPS as evidenced by publications on incident cases over the last 10 years. According to the Scottish Registry data, after four years on PD there is a one in twelve chance of developing EPS. The authors do not describe how the risk information can be communicated but do highlight the challenges, recommending at four years, a young patient who is suitable for transplantation should be taken off PD; whereas an elderly patient whose overall survival is reduced and not suitable for transplantation could remain on PD.

Early detection

There are difficulties in how best to detect early signs of EPS as often present as mild gastrointestinal features that are unreported and not seen as connected to EPS. The important factors relate to those patients at risk. At the moment in clinical practice there are no early diagnostic screening tools available. The use of routine CT scans has been proven to be unhelpful and nonspecific in the early stages. Evidence on the usefulness of MR scanning is not certain as yet. Other possible biomarkers or genetic predisposition have also not yet been developed. It is therefore crucial that HCPs listen to patients symptoms and concerns in particular those who have been receiving PD for over four years, especially if they have transferred to HD or been transplanted. Patient experience of EPS highlights the enormous burden of the disease and the problems patients have with early signs and symptoms not being recognised by HCPs. Surveillance and pathways for surgical referral are needed.

Treatment

Surgical

The most recognised treatment for EPS is surgery which usually includes total peritoneectomy and enterolysis. This meticulous procedure involves the entire small bowel from duodeno-jejunal flexure to ileo-caecal junction. The thickened parietal and visceral peritoneum is dissected from the underlying abdominal wall and small intestine respectively (peritoneectomy) with concomitant release of the associated small bowel obstruction (enterolysis). Techniques for surgery and findings intra-operatively highlight the complexities of EPS. It
is often a prolonged procedure with added complications such as haemorrhage, intestinal perforation, delayed wound healing and severe nutritional compromise. Risk of stoma formation is reported as 10% in Japan.

The main issue for surgical treatment is early referral, poorer outcomes are often seen in those patients referred when extremely acutely unwell. The requirements of these patients to be managed by specialist multidisciplinary teams (MDT) is now recognised, not only for surgical management but also pre-operative preparation and post-operative follow up. Once a patient develops early significant clinical features referral would enable the patient to be monitored by the surgical teams to allow planned surgery and early nutritional management. Only two centres in the UK offer this specialist surgery, located in Manchester and Cambridge. Across Europe more expertise is being developed as many patients from European countries come over to the UK for EPS surgery. Long term outcomes of patients who have undergone EPS surgery has yet to be published but reports are encouraging as many progress to successful transplantation following recovery from EPS.

One other aspect to consider for centres where patients return following EPS surgery is the careful monitoring for signs of recurrence and this has been reported up to be 15% in Japan. It is also important to understand the long term recovery period some patients need as they strive to return to normality.

Experiences of surgical treatment in Japan have been published, including extensive surgery to treat encapsulation and bowel obstruction. One report of 50 patients showed 4% postoperative mortality and 96% survival after three years, a significant improvement over previously published historical studies indicating high mortality at 100% for PD > 15 years. These studies were published over 15 years ago when surgical techniques were perhaps not as available or refined and diagnosis was delayed. More recently, studies reporting incidence of EPS using case control matches have found no difference in mortality in patients on PD with or without EPS, but in many cases co-morbidities are not given for either group.

Pharmacological
Pharmacological treatments have been reported only in a small number of cases and little evidence can be deduced about their effectiveness. Those most commonly reported are tamoxifen, corticosteroids and immunosuppressant therapies. There tends to be an emphasis on nutritional management and support, since this is effective in allowing the bowel to rest. A recent publication highlighted treatment of EPS with nutritional support to patients who were not referred for surgery but treated conservatively. This study emphasised the importance of nutritional support but currently there are no publications which demonstrate whether this treatment is preferable to surgery. It is however an essential preoperative requirement for patients about to undergo surgery, since the majority of patients presenting tend to be malnourished.

Implications for Clinical Practice
When considering the risk factors of EPS there is a general consensus that the increased awareness has had a negative impact on the uptake of PD. However, there are a number of factors to be borne in mind. The average length of time for patients to remain on PD is estimated to be two years, meaning that after two years only 50% will still be on PD. Patients who reach the four-five-year point will be relatively low but will vary from unit to unit. This raises questions about whether discussing the risk of EPS when a patient is starting dialysis treatment is appropriate. Furthermore, there are many other competing risks that outweigh those posed by EPS, such as cardiovascular disease. It has recently been suggested that a development of a competitive risk score concerning an individual’s likelihood of developing EPS would be more useful and is currently being developed in the UK.

EPS is an important condition, since it can result in prolonged debilitating illness. As previously mentioned, it may be a significant barrier to long-term PD treatment. It seems to have a disproportionately negative impact on clinicians’ perception of PD as a therapy for ESRD, compared with equally frequent and more severe therapy-specific complications in haemodialysis. The following factors have been recommended by ISPD in considering the risks mentioned:-

- Age and prognosis of patient;
- Length of time on PD, especially total glucose load and history of peritoneal infections;
- Access to and suitability for transplantation;
- Potential risk of HD in this particular patient (haemodynamic stability, vascular access); and
- Quality of life of the patient.

All these items should be discussed and any decision should be agreed with the patient.

Other aspects that are important to patient management are education and information. Patients receiving PD strive for independence and normality and are often reluctant to switch to HD. Patients that are deemed at risk are usually younger and therefore should be considered for home HD where possible to enable them to continue with a home therapy. Arming patients with information on the early signs and symptoms of EPS is also important as this empowers them.

Key messages for Clinical Practice can be seen in Table 2.

Table 2

<table>
<thead>
<tr>
<th>Key Messages for Clinical Practice</th>
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<tbody>
<tr>
<td>Understand the risk factors for EPS and formulate assessment plans and follow up for those patients, particularly when converted to HD</td>
</tr>
<tr>
<td>Be open and honest with patients about EPS discussing the early signs and symptoms</td>
</tr>
<tr>
<td>Refer early to specialist EPS centre for surgical opinion and soon as signs and symptoms present</td>
</tr>
<tr>
<td>Remember EPS is rare and most patients will not be at risk, therefore do not use EPS as a barrier to PD therapy</td>
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Summary

EPS still remains a rare complication of PD and can be catastrophic. Whilst the scientific community continue to research and examine factors that may influence early detection, prevention, risks and treatment, HCPs need to listen to patients and pay particular attention to the early signs of EPS.

Case Study Scenario and Questions

A 45 year old female patient has been receiving PD for 4.5 years with a history of two episodes of peritonitis in the past and recent loss of residual renal function. She is a fast transporter (signs of ultra-filtration failure evident) and is struggling with fluid overload and using dialysate with more glucose. She wishes to remain independent and is transferred to home HD.

After being at home for 8 months she has frequent episodes of vomiting and dropping her BP on dialysis. Her GP has referred her for a gastroscopy to investigate the vomiting. With guidance from the community dialysis nurse she manages the hypotension by adjusting her target weight as she is clearly becoming dehydrated. No other referral or discussion with the MDT is made. This continued for a further six months.

Questions

On initial reporting of her symptoms:-
1. What history is important at this stage?
2. Who should she have been referred to?
3. What investigations would be necessary?
4. What discussions should be had with patient?
   (See appendix One for answers and outcome)
References


Appendix One Answers

1. Full gastrointestinal history and review by dietician
2. Full medical review
3. Full set of blood tests including CRP
4. Abdominal examination and a contrast enhanced CT scan
5. Referral to surgeons within specialist centre with suspected early signs of EPS.
6. Inform the patient of the suspected diagnosis

She eventually came into hospital as she had developed ascites and features of intestinal obstruction and was referred immediately to the surgeons (within the specialist centre) and underwent EPS surgery within 2 weeks. Fortunately she made a full recovery and has since undergone transplantation.