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SPECIAL REPORT

The Dutch EPS Registry: Increasing the knowledge of encapsulating peritoneal sclerosis

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ABSTRACT

Encapsulating peritoneal sclerosis (EPS) is a rare condition characterised by fibrotic thickening of the visceral peritoneum, leading to encapsulating of the intestines with partial or total intestinal obstruction. EPS is a serious complication of peritoneal dialysis (PD) with high morbidity and a mortality exceeding 50%. At present, there is uncertainty concerning the incidence and the risk factors involved in the development of EPS. To address these questions a nationwide registry has been initiated.

The primary goals of the registry are to record the incidence of EPS and investigate the association of different variables, such as PD duration, medication, dialysis solutions and kidney transplantation with EPS.

The registry will improve the knowledge of EPS and will serve to develop guidelines and necessary management strategies. From the registry different research activities can be initiated. A major challenge lies in the establishment of criteria that allow a timely diagnosis of EPS. At present, there are no diagnostic tools that can accurately detect EPS at an early stage. For this reason, besides patients with proven EPS, the clinical suspicion of EPS will be a sufficient criterion for inclusion in the registry. This nationwide EPS registry is currently enrolling patients.

KEYWORDS

EPS, incidence, registry, risk factors

INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) is a clinical syndrome characterised by intestinal encapsulating and subsequent obstruction of the intestinal tract.[1] EPS can be found in many different clinical settings, but the condition is most frequently encountered in patients treated with peritoneal dialysis.

Although rare, EPS has come to be recognised as a serious complication of peritoneal dialysis (PD) with a high morbidity and a mortality of approximately 50%.[2]

Reported prevalences for EPS range from 0.7 to 3.3%.[2-4] Recently, more attention has been given to this complication, as several reports have suggested an increased incidence of EPS during the last years.[5,6]

PD is an excellent modality of renal replacement therapy (RRT) and may have a superior patient survival compared with haemodialysis,[7] due to a better preservation of the renal residual function.[8] In the period 1996-2006 approximately 7800 patients with end-stage renal disease were treated with PD in the Netherlands (Renine database). However, in recent years a worldwide trend of treating fewer patients with PD has been noted. Among other reasons, an increased fear of EPS may be an incentive for the nephrologist to favour haemodialysis over PD when starting renal replacement therapy.[9]

There is much uncertainty concerning the true incidence of EPS in the Netherlands. In addition, the clinical factors associated with the development of EPS seem to differ from previous reports, as we found a substantial number of severe cases of EPS after renal transplantation.[6]

Given the severity of the condition and the current lack of data, a collaboration was started among Dutch nephrologists, which has resulted in the initiation of a nationwide registry for EPS.

DISCUSSION

Clinical spectrum of EPS

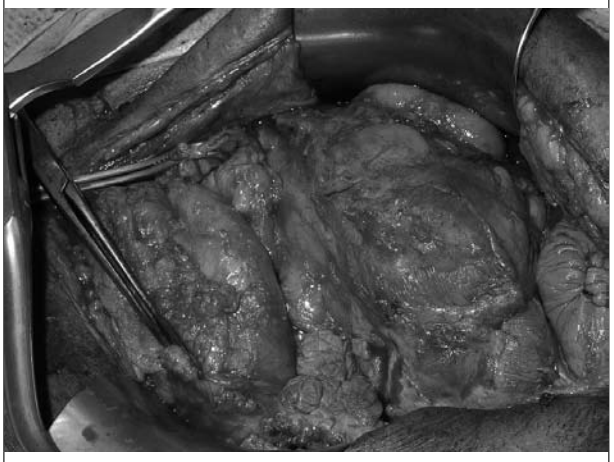
EPS, formerly known as sclerosing peritonitis, is characterised by progressive fibrosis of the visceral peritoneum resulting in a partial or total encasement of the bowel by a thickened and fibrotic membrane (*figure 1*).

The development of EPS is insidious and initially there are only vague abdominal complaints. With progressive fibrosis, symptoms as nausea, vomiting, appetite loss, weight loss and constipation appear. Usually, ultrafiltration failure has developed and signs of a systemic inflammatory syndrome may be present. Eventually, in the last stage of abdominal cocooning, there is partial or complete intestinal obstruction. At this stage there is a high morbidity and mortality. Recently, we performed a multicentre study in which we analysed the data of 2022 PD patients in the period 1996-2006. The results showed a high mortality rate for EPS, in accordance with studies from other countries (*figure 2*) (manuscript submitted).

The diagnosis of EPS is difficult because the criteria defined by the International Society for Peritoneal Dialysis (ISPD) (*table 1*) are rather aspecific.[10] The key feature of EPS is the presence of a clinical syndrome of intermittent or recurrent intestinal obstruction, with or without inflammation parameters. The existence of peritoneal thickening, sclerosis, calcifications and encapsulation is confirmed by macroscopic inspection or radiological findings.

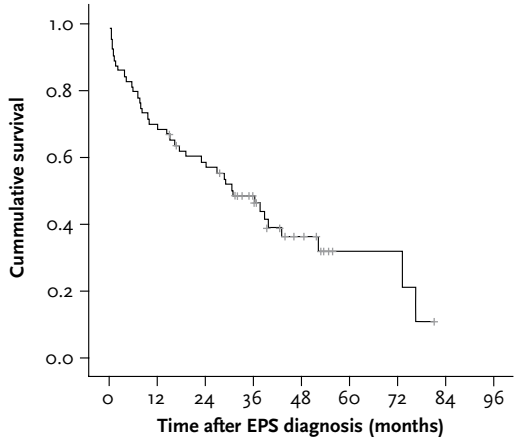
There is, however, a large overlap with simple sclerosis when patients are on PD for a longer time and CT scanning is not useful as a screening tool for early stages of EPS.[11] The use of macroscopic evidence of EPS is the only appropriate tool serving as golden standard for the diagnosis of EPS. However, this approach is not always feasible in a clinical setting and macroscopic evidence of EPS is only obtained in the minority of cases.

Figure 1. *Macroscopical encapsulating peritoneal sclerosis*



This patient with a history of PD has developed symptoms of intestinal obstruction. At laparotomy there is a clear fibrotic and thickened membrane covering the bowel. There are also extensive adhesions.

Figure 2. *Survival of patients with encapsulating peritoneal sclerosis*



In a Dutch multicentre study in the period 1996-2007 there were 63 patients with severe EPS in a total of 2022 PD patients. This figure shows the cumulative survival (Kaplan-Meier analysis) of these patients after the diagnosis of EPS was made.

Table 1. *Criteria for the diagnosis of encapsulating peritoneal sclerosis (EPS)*

ISPD[1]	**Criteria**
EPS	Intestinal obstruction[2] and radiological or macroscopical evidence[3]
EPS registry	
Macroscopial EPS (golden standard)	Intestinal obstruction[2] and macroscopically identified EPS
Clinical EPS	Intestinal obstruction[2] and radiological EPS[3]
Suspected early EPS	Intestinal obstruction or two or more findings of: • Weight or appetite loss • Bloody ascites • Radiological suggestion of EPS • Fast transport status or ultrafiltration failure
No EPS	Intestinal obstruction but other cause then EPS identified with certainty

[1]Criteria as used in the definitions by the International Society of Peritoneal Dialysis (ISPD) and the EPS registry of EPS in a patient that is currently being treated or has been treated with PD.[10] [2]Intestinal obstruction means any sign and symptom of persistent, intermittent or recurrent intestinal obstruction. [3]Radiological evidence for EPS means fulfilment of the criteria for EPS with CT scanning with findings such as peritoneal calcification, bowel thickening, bowel tethering, bowel dilatation, ascites or peritoneal thickening.[11]

Pathophysiology

The peritoneum of patients treated with PD is exposed daily to various dialysis fluids. This leads to changes of the peritoneal membrane over time characterised by mesothelial cell loss, epithelial to mesenchymal

transition of mesothelial cells, neovascularisation and vasculopathy.[12-16] These changes are probably induced by conventional dialysis fluids with bio-incompatible characteristics, high glucose concentrations, glucose degradation products, lactate buffers and acid pH. This process during long-term PD with fibrosis of parietal peritoneum is sometimes referred to as simple sclerosis.[17] It is generally assumed that the abundant fibrosis of the visceral peritoneal as seen in EPS, has a different aetiology to simple sclerosis. The complete pathophysiology of EPS is still unclear, but is probably multifactorial. The duration of PD is recognised as the single most important risk factor for EPS, as EPS within three years of treatment is rarely observed. Therefore, the most generally accepted theory assumes a progressively damaged peritoneum by prolonged use of incompatible dialysis fluids, which may be complicated by factors that aggravate the peritoneal sclerosis.[4,18] In recent years candidate factors came forth from a number of observational studies. These included cessation of peritoneal lavage,[3] peritonitis[19,20] and factors associated with kidney transplantation.[6]

Why a nationwide registry?

To date, there are still large gaps in our knowledge of EPS. This can be largely attributed to the lack of systemic prospective data collection, specifically necessary in the case of a condition encountered less than once a year in an average dialysis centre. Such a data collection is even more important as we reported a possible increased incidence of EPS.[5] Therefore, the first goal of this registry should be to record the current incidence of EPS and investigate whether it is still increasing.

Secondly, the registry needs to investigate the association of different variables, such as PD duration, medication, dialysis solutions and kidney transplantation. For instance, our case-controlled analysis of EPS cases in the Netherlands over the last ten years showed a strikingly high percentage of EPS (50%) shortly after renal transplantation and suggested that the use of icodextrin was independently associated with EPS (data unpublished). In addition, the statistical modelling indicated that a large part of the variation was not accounted for by the clinical and demographical variables used for analysis. These observations, which may have major consequences for the management of the PD patients, need to be verified in a prospective database. Furthermore, in an effort to document early stages of EPS we will also include cases of suspected EPS. This also allows identification of risk factors for progression and discovery of biomarkers for establishing EPS at an early stage.

In a recent survey among Dutch nephrologists it appeared that 16% of the responders feared EPS and subsequently considered withholding PD as a first choice of RRT.[9] Given the rarity of the disease and good overall survival on PD this decision is illogical, but illustrates the need for a registry recording data and yielding evidence-based guidelines to the treating physicians. As such, these data are currently not available and there is a lack of prospective studies on EPS. The majority of the experience comes from Japanese observational studies, where patients tend to be on PD for a longer period because the limited availability of kidney transplantation.[8] It is not clear whether the Japanese findings can be extrapolated to the PD population of Western Europe.

An important part of the guidelines is the development of an uniform management strategy for EPS. As malnutrition occurs in the presence of intestinal obstruction, supportive care with either enteral or parenteral nutrition is the mainstay of the treatment.[21] Immune suppressive medication and others agents, such as tamoxifen, have been suggested.[22-25] But the level of evidence is low as the data are from anecdotal reports or small case series. Encouraging results from Japan have been reported with surgical enterolysis, releasing the complete small intestine.[26] However, there is still little experience with this procedure in Western Europe. Finally, the registry will function as a central organisation from which different research activities, for example genetic and marker studies, can be initiated. To strengthen the importance of the registry there will be extensive collaboration within Europe, for instance with the UK EPS study group.

Design

Collaboration of all university centres and the Hans Mak Institute resulted in a steering committee, which has initiated the nationwide EPS registry. Patients with a history of PD with a diagnosis of EPS or suspicion of EPS will be prospectively included. Ideally, the registry would include all patients treated with PD. This way, all data could be accurately registered. However, given the low prevalence of EPS, inclusion of all PD patients would be time consuming and requires a very large, expensive database.

Every six months an e-mail will be sent to all Dutch nephrologists inquiring whether they can report a patient (suspected of) having EPS. In the registry patients are divided into four groups by the steering committee; macroscopically definite EPS, clinical EPS, possible EPS and no EPS, by the criteria shown in *table 1*. As multiple factors may influence the development of EPS, there will be an extensive review of all possible diagnostic, prognostic and therapeutic variables. Demographics, and factors related to PD, HD and transplantation for all included patients will be reviewed. In addition, a sample of peritoneal effluent and plasma will be taken and stored for later analysis.

An easy accessible website (www.epsregistry.com) has been developed to give more detailed information on EPS and the EPS registry. The registry is set up so that it can easily be extended to a European format.

For professionals it also has the opportunity to submit a patient with EPS. There will be a yearly update on the progress of the registry. In the future research developments and guidelines will be published on the website.

CONCLUSION

EPS is a potentially devastating disease with a high mortality. Recently, it was shown that the prevalence of EPS may increase in the Netherlands. The low prevalence of EPS has hampered the research in this area, which has resulted in a lack of knowledge about natural history, pathophysiology and risk factors, and treatment options. A nationwide registry is required to collect data prospectively. Such an EPS registry was recently initiated. The database of this EPS registry will allow establishment and monitoring of the prevalence of EPS, identifying risk factors, basic research on the pathophysiology of EPS and development of management guidelines. The EPS registry is currently enrolling patients. We kindly call upon all nephrologists to cooperate with the registry in order to obtain a representative registry and thus contribute to a better understanding of EPS.

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