Encapsulating peritoneal sclerosis: early diagnosis and risk factors
Sampimon, D.E.

Citation for published version (APA):
INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) is a severe complication of peritoneal dialysis (PD). The present thesis focused on different aspects of this condition. This thesis consists of three parts: EPS and risk factors, EPS and early diagnosis, and EPS and animals models.

In this final chapter the general results are summarized and discussed.

SUMMARY OF CHAPTER

In Chapter 2 the general aspects of PD and EPS have been discussed. A review of EPS has been given in Chapter 3, aimed at clinical working nephrologists.

In Chapter 4 we investigated risk factors of EPS in all PD centers in the Netherlands. The objective of this study was to determine the prevalence and risk factors for the development of EPS. The prevalence of EPS was 2.7%. Risk factors that independently associated with EPS were cumulative time on PD, age at start PD, transplantation, time since last transplantation until EPS or discontinuation of PD, calendar time, period of using icodextrin and presence of ultrafiltration failure (ultrafiltration failure).

In Chapter 5 we have studied Alport syndrome as a risk factor for EPS. Out of 13 EPS patients 2 had Alport syndrome as a primary kidney disease. Both conditions are considered rare and joint occurrence would be highly unlikely. We have discussed a hypothesis of genetic predisposition of patients with Alport syndrome to develop EPS. Alport syndrome patients miss collagen IV in their basement membranes and in the skin this is replaced by collagen VII, found often in scar tissue. We hypothesized that this replacement of collagen IV by collagen VII in the skin could also occur in peritoneal tissues.

Possible prevention of EPS by angiotensin II inhibitors has been described in Chapter 6. The rationale for this study was that angiotensin II inhibitors appear to prevent renal fibrosis. Animal studies have shown that EPS is prevented by exposing the animals to angiotensin II inhibitors. The median duration of ACEi/ARB use expressed as a percentage of total PD time was 16% for EPS patients and 41% for controls. Statistical significance was not reached, probably due to the small number of patients.

Chapter 7 describes the time course of different peritoneal transport parameters prior to the development of EPS. The time course of small solutes showed an initial increase. One year prior to the diagnosis of EPS a decrease in small solute transport was present. The time course of fluid transport showed a linear decrease in time. In Chapter 8 we compared these time courses to those in control patients. The time course of small solutes and fluid transport was different between EPS patients and patients with normal ultrafiltration. However no distinction could be made between the time courses of EPS patients and patients with ultrafiltration failure. The effective lymphatic absorption rate showed overall lower values in EPS patients than in ultrafiltration failure patients. This functional abnormality was present in almost all patients 6 months prior to the diagnosis of EPS. An additional analysis was performed with a definition of ultrafiltration failure of less than 400mL/4h/3.86% glucose with an intra individual coefficient of variation of 17% (net ultrafiltration = 470mL/4h/3.86%). All patients had ultrafiltration failure according to this definition 6 months prior to the diagnosis EPS. The presence of late ultrafiltration failure was an important risk factor for the development of EPS. Half of the patients that continued PD for 2 years after late ultrafiltration failure was diagnosed developed EPS.

Early diagnostic effluents markers for EPS were investigated in Chapter 9. This
study showed that K+ and vascular endothelial growth factor (VEGF) are not useful for making a diagnosis of EPS. However, the combination of the appearance rate (AR) interleukin-6 (IL-6) and AR cancer antigen-125 (CA-125) in patients with ultrafiltration failure gave a sensitivity of 70% and a specificity of almost 100% for the diagnosis of EPS. Obviously, these results need to be confirmed in a different PD population.

Experimental models are important to study a disease. In chapter 10 and 11 two attempts to develop a clinical relevant EPS model have been made. The renal failure and daily exposure to conventional dialysis fluids were applied in both models. In Chapter 10 chlorhexidine gluconate was added to the dialysis fluid. Chlorhexidine overruled the effect of dialysis fluids, even though a very low dose was applied. Therefore, chlorhexidine should not be used in experimental peritoneal sclerosis model anymore. In Chapter 11 a single dose of intraperitoneal blood was administered after 8 weeks. Numerous intraperitoneal adhesions developed as seen in EPS, but without cocoon formation. Microscopically no differences were present in fibrosis scores and vessel counts between the experimental and control groups.

GENERAL DISCUSSION

Risk factors
Duration of PD remains the most important risk factor in the development of EPS. A rise in the number of EPS patients was found in the multi center study (Chapter 4), although the number of PD patients decreased. This increase in EPS incidence was also described in other studies and believed to be caused by kidney transplantations. The number of kidney transplantations has increased in the recent years. The multi center study reported that the risk on EPS increased in the first year after transplantation up to 7.5%.

EPS often develops after the discontinuation of PD treatment. The lack of washing out and removal of fibrin, growth factors and cytokines has been suggested as its main cause. This may also explain the increased risk in the first year after transplantation. Calcineurin inhibitors prescribed for immunosuppressive therapy after transplantation have also been suggested as risk factors for EPS. These drugs cause upregulation of transforming growth factor beta and other profibrotic proteins and thereby stimulate fibrosis synthesis. Case-reports have described the development of EPS after a liver transplantation with the use of tacrolimus in patients not exposed to PD treatment.

In the AMC population, EPS patients were younger than most PD patients. The multi center study (Chapter 4) demonstrated that young age was a risk factor. Recently an Australian EPS multi center study confirmed this risk factor. Because the objective of our study was to reveal risk factors and not study the causative pathway, we can only speculate on the meaning of this “risk factor”. Young age 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. Young patients in general are the ones who have the best survival benefit on PD over hemodialysis. Only a small percentage develops EPS. This study also included an unexpected risk factor. Duration of icodextrin use was a risk factor even when adjusting for ultrafiltration failure. However, in the present multicenter study ultrafiltration failure was defined mostly on the clinical presentation with overhydration, not on the definition of the International Society of Peritoneal Dialysis (ISPD) of a net ultrafiltration of less than 400mL during a 3.86% glucose dwell lasting for 4 hours. Icodextrin is often prescribed
Summary and general discussion

to patients with a poor ultrafiltration status and may have been a substitute marker for ultrafiltration failure in this study. We made it likely in this thesis that ultrafiltration failure is an important risk factor for the development of EPS.

Genetic predisposition may be of great importance for the development of EPS. This thesis suggested an increased susceptibility of Alport syndrome patients to the development of fibrosis and sclerosis (Chapter 5). Other genetic backgrounds may also be of influence. In the effluent marker study high values for IL-6 were found (Chapter 9). The genetic background can influence the concentration of this cytokine in dialysate and serum. Currently, a DNA database is build that enables further studies.

Inhibitors of the renin-angiotensin system have a protective effect on the peritoneal membrane in animal models and has been suggested in humans. Patients treated with ACEi/ARBs for 75% of their time on PD showed decreased small solute clearances compared to controls. In our center, EPS patients were exposed to ACEi/ARBs for a shorter duration of their PD treatment compared to matched controls, however not statistically significant. The inhibiting influence of ACEi/ARBs on the development of fibrosis has been demonstrated in many experimental and in vitro studies. Therefore larger patient studies on the effect of ACEi/ARB on peritoneal fibrosis in humans are required.

**EARLY DIAGNOSIS**

The clinical presentation of overt EPS often has a long previous history. Abdominal complaints, nausea and complaints of changing defecation may be present for months. We can conclude that EPS usually does not appear suddenly but develops over a period of time. This is the rationale of studying early diagnostic markers of EPS. In this thesis we studied the preceding stages of EPS in peritoneal function and effluent. This was possible because in our center peritoneal function tests are performed yearly after which effluent and serum samples are stored. As a result, we were able to study data up to 6 months prior to the diagnosis.

The results of Chapter 8 showed that when PD is continued and ultrafiltration failure is present, the risk on EPS increases up to 50%. Our results also demonstrate that it is difficult to distinguish patients that will develop EPS form patients that have ultrafiltration failure but will not develop EPS. The time courses of solute transport parameters in patients with ultrafiltration failure are similar between those that develop EPS and those who did not. Fast solute rates are merely a sign of peritoneal angiogenesis present most patients with ultrafiltration failure. Follow-up of the peritoneal function is important and it should be performed with a 3.86% glucose dwell.

Two effluent markers we studied were successful in making an early diagnosis of EPS (Chapter 9). The AR of CA-125 and IL-6 in combination of ultrafiltration failure had a sensitivity of 70% and a specificity of almost 100% for the diagnosis of EPS a year prior to the clinical presentation. This makes sense because in EPS a disappearance of the mesothelial cell layer has been described and therefore low effluent CA-125 levels were not unexpected. Besides, it has been suggested that an inflammatory state may precede the encapsulation of the intestines. The increase in effluent IL-6 levels is in line this theory. However, the study aimed to analyze risk factors, not the causative agent. Effluent VEGF values increase with the duration of PD. A contribution of VEGF in epithelial-to-mesenchymal-transition is likely. However, we could not demonstrate
Summary and general discussion

an effect of VEGF prior to the development of EPS. Most likely, this was a result of the low number of data on locally produced VEGF.

RECOMMENDATIONS

Previous studies have advised to discontinue PD treatment after 5 years. We disagree because we believe the high risk on EPS only develops when late ultrafiltration failure is present and AR CA-125 levels are below 33 U/min and AR-IL-6 levels are above 350 pg/min. Based on the results discussed in the present thesis our recommendations are as follows:

1. Peritoneal function with a 3.86% glucose dwell and AR-CA-125 and AR-IL-6 should be measured on a yearly basis.
2. When a patient develops late ultrafiltration failure, PD should be discontinued within 2 years.
3. When the appearance rate of CA-125 drops below 33 and AR Il-6 levels are higher than 350, PD should be discontinued.
4. When PD is discontinued due to the above mentioned reasons, tamoxifen treatment should be considered.
Summary and general discussion

REFERENCE LIST


Summary and general discussion


