Encapsulating peritoneal sclerosis: early diagnosis and risk factors
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CHAPTER 2

GENERAL INTRODUCTION, AIMS AND OUTLINE OF THIS THESIS
CHRONIC KIDNEY FAILURE AND PERITONEAL DIALYSIS

When chronic kidney failure develops the kidney function needs to be replaced. This can be achieved with kidney transplantation, hemodialysis or peritoneal dialysis (PD). In the Netherlands about 2000 new patients develop chronic kidney failure each year. In 2008 over 13000 patients needed renal replacement therapy, of which 55% had a functioning donor kidney, 35% was treated with hemodialysis, and 10% underwent PD therapy. In the recent years, the proportion of dialysis patients treated with PD has decreased from 30% in 2002 to 20% in 2008. The decrease in PD is regrettable because the overall survival of PD patients, especially non-diabetic patients, is better in the first years of dialysis treatment compared to hemodialysis patients. The cause of this decline is unclear but a recent survey among Dutch nephrologists revealed the fear of a rare complication of PD, encapsulating peritoneal sclerosis (EPS), as a possible contributor to this trend.

ENCAPSULATING PERITONEAL SCLEROSIS

EPS is the most severe complication of long-term PD. EPS causes the peritoneum to become a thick fibrous membrane that covers the intestines and causes their dysfunction leading to intestinal obstruction. This complication is rare and the reported prevalence varies between 0.5% and 2.5%. However, EPS mortality rates are up to 50%. There are still a number of issues that need to be clarified about EPS for instance the pathophysiological process, which PD patients are prone to developing EPS and how to prevent EPS.

PERITONEAL DIALYSIS AND THE PERITONEAL MEMBRANE

In PD the peritoneal membrane is used as a dialysis membrane and functions like a semi-permeable membrane. Excess fluid and waste products are removed with help of dialysis fluids. These dialysis fluids are infused in the peritoneal cavity several times a day through an abdominal catheter. The peritoneal membrane is lined by a continuous sheet of mesothelial cells. The mesothelial cells separate the peritoneal membrane from the peritoneal cavity. Between the mesothelial layer and the vascular plexus lays the submesothelial compact zone which consists of bundles of collagen fibres loosely arranged and interwoven with occasional elastin fibers. Macrophages and fibroblasts are dispersed throughout this compact zone. Alterations in the morphology occur with the course of PD because the peritoneum is a physiological membrane. The peritoneum consists of a visceral and parietal part. The visceral peritoneum covers the intestines, while the parietal peritoneum lines the inner abdominal wall. The space in between is the peritoneal cavity.

PERITONEAL PERMEABILITY

During peritoneal dialysis, excess water and waste products are removed from the circulation through convection and diffusion. Diffusion is based upon a difference...
in solute concentrations between two compartments. Convection or solvent drag is transport of solutes associated with fluid movement. The peritoneal membrane is a size-selective barrier that restricts the transport of solutes according to their molecular weight. This feature is the intrinsic permeability of the peritoneal membrane. The peritoneal permeability is determined by the capillary wall and surrounding tissues. Low molecular weight solutes are transported through diffusion. They are unrestricted by their size and reflect the number of perfused capillaries and consequently the effective surface area. The surface area of the peritoneal membrane and its intrinsic permeability are the major determinants of peritoneal permeability.

Water transport during PD is dependent on the hydrostatic and osmotic pressure gradients, and on absorption from the abdominal cavity by the lymphatics. The removal of excess water or ultrafiltration is one of the main objectives of PD. Water is pushed into the peritoneal cavity by the hydrostatic pressure in the capillaries of the peritoneal membrane. The re-uptake due to osmotic colloid pressure is prevented by the osmotic agent in the dialysate. Thereby net ultrafiltration is obtained.

The peritoneal permeability or function can be measured by a standard peritoneal permeability analysis (SPA) or a peritoneal quilibrium test (PET) during a 4 hour dwell. The International Society of Peritoneal Dialysis committee on ultrafiltration management in PD suggested to perform the test with a 3.86% glucose solution, because this provides better information on ultrafiltration and its mechanisms.

LONG-TERM PERITONEAL DIALYSIS

The peritoneal membrane changes with the duration of PD. This is for a large part caused by the continuous exposure to dialysis fluids especially glucose and glucose gradation products (GDPs) that are formed during heat sterilization. The mesothelial layer disappears or degenerates and the submesothelial compact zone becomes thicker. New vessels develop and the vessels become damaged. These changes in peritoneal structures may be detected by alterations in peritoneal function. With the duration of PD the effective peritoneal surface area increases most likely due to neoangiogenesis and dilatation of the vessels. This is reflected by fast solute transport rates. Another feature of long-term PD is the restricted intrinsic permeability of the membrane. The peritoneum becomes less permeable with the duration of PD. The increase of solute transport and decrease in water transport is associated with time on PD. It has been suggested that the increased small solute transport rate induces a faster absorption of glucose which causes an early dissipation of the osmotic gradient with ultrafiltration failure as a consequence.

The changes in peritoneal structures may also be detected by effluent markers such as cytokines and growth factors. For instance, cancer antigen-125 that reflects the mesothelial cell mass. With the duration of PD the CA-125 levels decrease similar to the disappearance of the mesothelial cell mass.

RISK FACTORS OF EPS

Many peritoneal alterations and EPS are thought to be caused by exposure to dialysis fluids. As a result more biocompatible fluids have been developed. These solutions have a reduced content of GDPs and use bicarbonate as a buffer. They are kept in
two compartment bags which are mixed just before the inflow in order to prevent the development of GDPs. Also alternatives to glucose as an osmotic agent have been developed. Icodextrin is a glucose polymer and dialysate solutions with this osmotic agent are prescribed in order to keep the glucose exposure low.

Although the exposure to dialysis solutions is an important risk factor for the development of EPS, not all long-term PD patients develop EPS. Therefore there must be other factors that can cause EPS. For instance genetic predisposition may be important in the development or prevention of EPS.

The use of angiotensin II inhibitors is associated with preservation of the residual renal function. In PD patients the use of angiotensin II inhibitors prevented the increase in solute transport rates commonly seen in long-term PD. Animal studies have reported a beneficial effect of angiotensin II inhibitors on the development of fibrosis in the peritoneum. It is unknown whether angiotensin II inhibitors prevent peritoneal fibrosis in humans.

AIM AND OUTLINE OF THE THESIS

The main objective of this thesis was to investigate the early stages of EPS. Once the early stages of EPS have been recognized, therapy to prevent EPS can start.

This Chapter 2 gives a short general introduction to this thesis. In Chapter 3 an extensive review on all the different aspects of EPS is given. In this chapter, we aimed to give a complete summary of the literature on EPS to keep nephrologists up to date. Chapter 4 is a multicenter study on EPS performed in the Dutch PD population. In total 63 EPS patients and 126 control patients were included. Different risk factors of EPS were identified.

The exposure to bioincompatible dialysis fluids is considered the most important risk factor for the development of EPS. However, in Chapter 5 a patient is described who developed EPS despite the exclusive use of biocompatible fluids. This chapter reports Alport syndrome as a possible genetic predisposition to the development of EPS.

Whether angiotensin II inhibitors prevent the development of peritoneal fibrosis has been studied in animal models, but not in humans. In Chapter 6 we investigated whether the duration of exposure to angiotensin II inhibitors in EPS patients was less than in controls that did not develop EPS.

The peritoneal changes during the development of EPS may be reflected by peritoneal transport characteristics and effluent markers. Chapter 7 studies the time course of different peritoneal transport parameters prior to the development of EPS. In Chapter 8 this analysis is repeated in the EPS group and compared to time courses of PD patients with and without ultrafiltration failure. Chapter 9 investigates different effluent markers prior to the development of EPS. Cancer antigen 125, interleukin-6, potassium and vascular endothelial growth factor were studied. Animal models of EPS are needed to understand more about this complication and to test different therapies. However clinical relevant model are still not available. Chapter 10 describes a peritoneal sclerosis animal model with renal failure exposed to dialysis fluids and chlorhexidine. Chapter 11 a “two-hit” approach was applied to develop an animal model of EPS.

Chapter 12 discusses all results obtained in the present thesis.
REFERENCE LIST


