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SHORT REPORTS

Significant Decreasing Incidence of Encapsulating Peritoneal Sclerosis in the Dutch Population of Peritoneal Dialysis Patients

The Dutch Encapsulating Peritoneal Sclerosis (EPS) Registry was started in 2009. Cases were identified by contacting all Dutch nephrologists twice yearly. The predefined criteria for EPS allowed for inclusion of patients with diagnosed and suspected EPS. Cases registered between January 2009 and January 2015 were analyzed with follow-up until September 2015. Fifty-three EPS cases were identified, of which 28.3% were post-transplantation EPS cases. Fourteen patients were initially categorized as suspected EPS, of whom 13 developed EPS. A remarkable 6-fold decrease in the yearly incidence of EPS was observed, from 0.85% in 2009 to 0.14% in 2014. This decrease could not be explained by a decrease in the number of PD patients or average duration of PD treatment in this period. Two-year survival of EPS patients was 52%. The use of tamoxifen and surgical interventions increased significantly over the years. Tamoxifen-treated cases showed a trend to better patient survival and post-transplantation EPS had a significantly favorable outcome. In conclusion, the incidence of EPS has declined significantly in the Netherlands from 2009 to 2014.

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KEY WORDS: Encapsulating peritoneal sclerosis; peritoneal dialysis; registry; tamoxifen.

Encapsulating peritoneal sclerosis (EPS) is a rare but potentially devastating complication of peritoneal dialysis (PD). The condition is characterized by the formation of an excessive fibrotic peritoneal membrane covering the bowel and causing bowel obstruction. Estimates of its prevalence in PD patients range from 0.7 – 3.7%, with a previous study among Dutch PD patients showing a prevalence of 2.7% (1,2). Encapsulating peritoneal sclerosis mortality rates range from 25.8 – 56.5%. The most important risk factor for developing EPS is PD duration. The number of peritonitis episodes while on PD and the type of PD solution have also been associated with the risk of developing EPS (2,3).

The majority of patients become symptomatic after cessation of PD treatment, e.g. after switching to HD or after undergoing a successful kidney transplantation. The latter is called post-transplantation EPS as opposed to the classical form of EPS (4).

Patients with EPS may present with intermittent bowel obstruction, after which the disease progresses to sustained

ileus (1,5). Patients often display ultrafiltration failure, bloody ascites and elevated C-reactive protein (CRP) levels (3). An abdominal computed tomography (CT) scan may show findings that indicate EPS, but the golden standard in diagnosing EPS is surgical exploration, which may reveal bowel adhesions and a thick fibrotic membrane covering the intestine (1). Pharmacological interventions include corticosteroids and tamoxifen, but peritonectomy and enterolysis may be necessary.

A nationwide effort to collect EPS data was started among Dutch nephrologists in 2009 by the establishment of the Dutch EPS registry (www.epsregistry.eu). One of the central roles of the registry is to prospectively collect data of all new confirmed and suspected cases of EPS in the Netherlands. In this study, we report on the results after 6 years of collecting data via the registry, with a focus on clinical characteristics and outcome.

METHODS

The Dutch EPS registry was approved by the ethical committee of the Erasmus medical center (METC). Peritoneal dialysis patients with a definite or suspected diagnosis of EPS were prospectively included after signing informed consent. These patients were all evaluated by the steering committee, which classified each case according to the criteria (Table 1) published by Korte *et al.* (6).

From 2009 onwards, every 6 months an email was sent to all Dutch nephrologists inquiring whether they had seen or suspected any new cases of EPS in their practice. Upon submission of a new case, data collection took place by trained research nurses or medical trainees. All gathered information was reviewed by the steering committee of the Dutch EPS registry to classify the submitted cases into the predefined categories. Following inclusion in the registry, a yearly update of clinical data was performed. This was either done by email, by phone, or by visiting the treatment center. The data from patients added to the registry from January 2009 until January 2015 were analyzed with a follow-up period until September 2015.

To determine the incidence of EPS among Dutch PD patients, we used data provided by the Dutch Renal Registry RENINE. The total number of patients treated with PD for more than 1 day within the Netherlands per year was used to calculate the incidence of EPS.

STATISTICAL ANALYSIS

Survival was plotted using Kaplan-Meier analysis in IBM SPSS 21. Differences between survival curves were analyzed

TABLE 1
Criteria for the Diagnosis of Encapsulating Peritoneal Sclerosis Used by the Dutch EPS Registry^a

Macroscopical EPS (golden standard)	Intestinal obstruction ^b and macroscopically identified EPS
Clinical EPS	Intestinal obstruction ^b and radiological EPS ^c
Suspected early EPS	Intestinal obstruction or 2 or more findings of: <ul style="list-style-type: none"> • Weight or appetite loss • Bloody ascites • Radiological suggestion of EPS • Fast transport status or ultrafiltration failure
No EPS	Intestinal obstruction but cause other than EPS identified with certainty

EPS = encapsulating peritoneal sclerosis; PD = peritoneal dialysis; CT = computed tomography.

^a Criteria as used by the International Society for Peritoneal Dialysis and the EPS registry in defining EPS in a patient who is currently being treated or has been treated with PD.

^b Intestinal obstruction means any sign and symptom of persistent, intermittent, or recurrent intestinal obstruction.

^c 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.

by log-rank test. The Cox proportional hazards model was applied to analyze the relation of covariates to the hazard of death after the diagnosis of EPS was established.

RESULTS

Patients Submitted to the Registry: The response rate to the emails ranged from 75% to 92%. All academic and major hospitals reported back to us. In January 2015, 58 patients were submitted to the registry with a possible diagnosis of EPS that was not diagnosed before January 2009. Fourteen patients were identified as suspected early EPS, 28 with clinical EPS, and 12 with macroscopic EPS. Four patients did not meet the criteria for EPS. Thirteen patients with suspected early EPS were at follow-up eventually diagnosed as having EPS, and macroscopic EPS was identified in 3 cases. Therefore, the total number of patients with EPS within the registry from January 2009 to January 2015 was 53 (Table 2).

After 2011, a drop in the number of new EPS patients was observed (Figure 1A), which led to a significant 6-fold decrease in the incidence of EPS, from 0.85% in 2009 to 0.14% in 2014 (Figure 1B and C). The average duration on PD of all Dutch PD patients between 2009 and 2014 remained stable (Figure 1D). Access to individual data of the RENINE registry is not allowed because of privacy regulations, but the percentage of patients on PD for more than 5 years steadily increased, from 7.6% in 2009 to 10% in 2014.

TABLE 2
Clinical Characteristics of Patients Included in the Dutch EPS Registry 2009–2014

Gender (male/female)	31/22
Age at diagnosis	56.9±14.8 years
Duration of PD treatment	65.3±32.5 months
Average number of peritonitis episodes	4.5±3.4
Median time until death after EPS diagnosis	28.3 months
Follow-up after EPS diagnosis	40.6±4.8 months
Post-transplantation EPS	28.3%
Underlying kidney disease	% of total EPS patients
Unknown	20.7%
Glomerulonephritis	22.7%
Diabetes mellitus	15.1%
Renovascular disease	20.8%
Cystic kidney disease	9.4%
Other	11.3%
Treatment for EPS	
Palliative care	7.5%
Parenteral nutrition	43.4%
Steroids/steroids and tamoxifen/ steroids and surgery	39.6% / 32.1% / 11.3%
Tamoxifen/tamoxifen and surgery	54.7% / 15.1%
Surgery/surgery without steroids or tamoxifen	34.0% / 15.1%

EPS = encapsulating peritoneal sclerosis; PD = peritoneal dialysis.

Clinical Characteristics of EPS Patients: Clinical characteristics of all EPS cases are shown in Table 2. One-year and 2-year survival for EPS patients was 67% and 52% (Figure 2A). In agreement with our previous findings, the post-transplantation EPS group had a much better survival rate after diagnosis than the classical EPS patients (Figure 2C) (7). The majority of patients received surgical and/or medical treatment, with tamoxifen given in over half of the patients. Survival of patients receiving tamoxifen was better although the *p* value was 0.058 for the difference in mortality (Figure 2B). Treatment with prednisone was not associated with better patient survival (Figure 2D). Surgical intervention was associated with better patient survival (Figure 2E) whether or not patients were also receiving tamoxifen or steroids (data not shown). Total parenteral nutrition (TPN) was associated with decreased patient survival (Figure 2F), reflecting more severe forms of EPS. Multivariate Cox regression analysis identified age (hazard ratio [HR] 1.06, *p* = 0.002), male gender (HR 2.32, *p* = 0.045), post-transplantation EPS (HR 0.33, *p* = 0.034), and tamoxifen treatment (HR 0.49, *p* = 0.082) as associated with patient survival. No significant interaction was observed between the different covariates.

The clinical characteristics of the suspected EPS group were similar to the data of the other patients, with an average age of 59 years, average PD duration of 59 months, and predominantly men (9 out of 13). Five out of 13 (38.4%) underwent EPS surgery, 8 (61.5%) were treated with tamoxifen, 2 (15.4%) received steroids (*p* < 0.03 compared with other EPS patients),

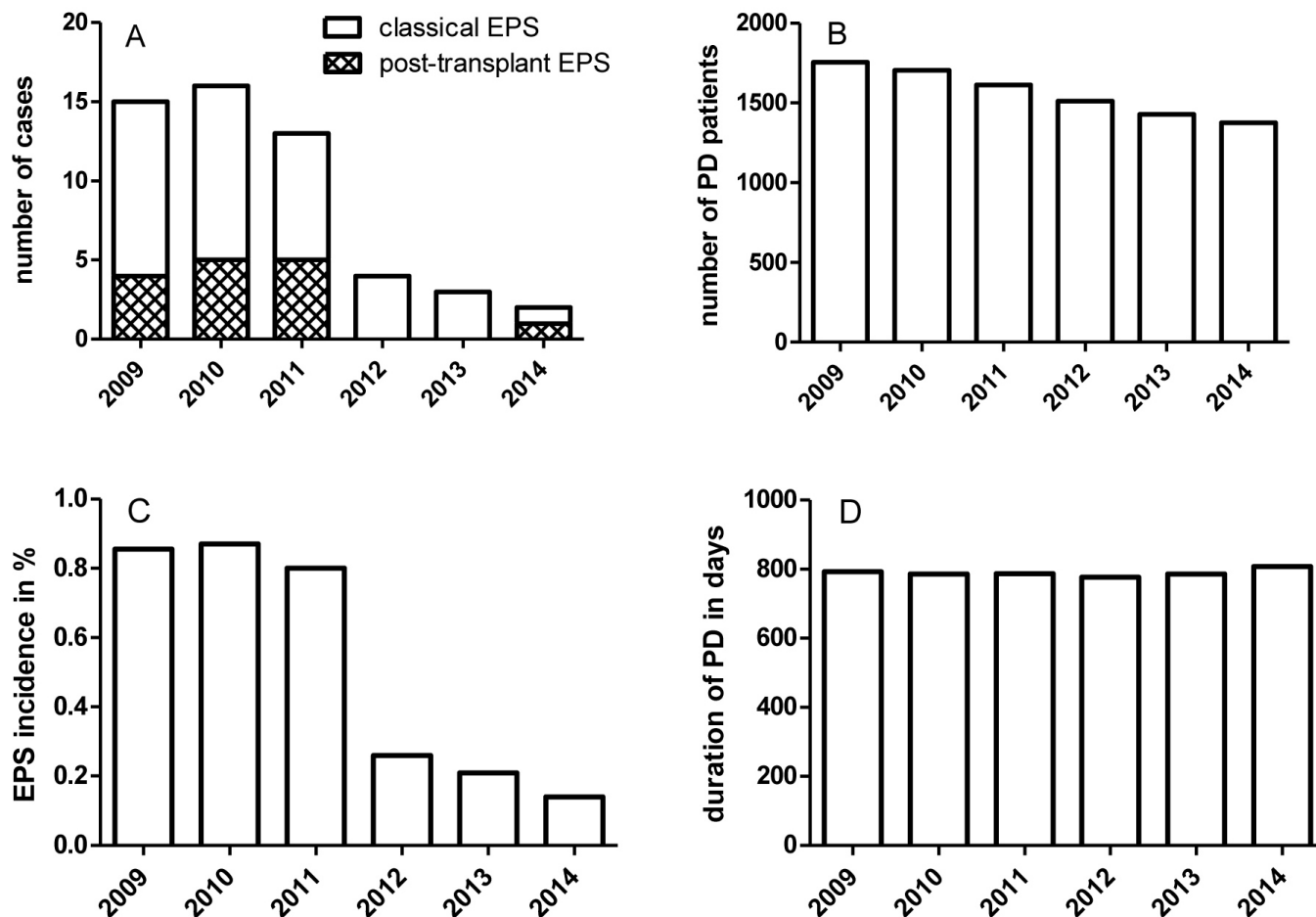


Figure 1 — A) The number of new cases of EPS registered within each year from January 2009 to January 2014, divided in the subgroups of classical and post-transplantation EPS. B) The total number of patients treated with PD for more than 1 day within the Netherlands per year between 2009–2014. C) The EPS incidence calculated for each year. D) The average number of treatment days for all PD patients in the Netherlands within each year (1D). EPS = encapsulating peritoneal sclerosis; PD = peritoneal dialysis.

and 4 (30.8%) were post-transplantation EPS patients. However, significantly fewer patients in the early suspected group received TPN (15.4% vs 52.5%, $p < 0.03$) and 1- and 2-year survival (84% and 84%) was better compared with the other EPS patients (70% and 44%, $p = 0.028$).

DISCUSSION

The results show a substantial decrease in the number of EPS cases from 2011 onwards. Previously, we found an EPS prevalence of 2.7% in the period 1996 to 2006 (2), with a significant rise in the number of EPS patients from 2001 onwards. This unexplained increase in EPS cases was actually one of the main reasons for the establishment of the Dutch EPS Registry (6).

The current series of cases confirms that EPS cases have on average a long duration of PD treatment. However, the average duration of PD in The Netherlands was stable between 2009 and 2014, and the number of long-term PD patients did not significantly change over time.

Changes over time in concentration of several biomarkers (4,8) have indicated an increased inflammation of the

peritoneal membrane several years before the clinical diagnosis of EPS. Thus, exposure to risk factors for EPS, such as certain dialysis fluids, should be considered in the context of all years of PD treatment. Unfortunately, incomplete registration of usage of PD fluids in the registered EPS patients prevented a meaningful analysis.

Remarkably, our observations are in accordance with recent Japanese data that document a decreasing number of new EPS patients in the last decade (5). The substantial decrease of EPS cases in Japan seems to be the result of a very low peritonitis incidence, strict use of biocompatible dialysis fluids only, and a policy of taking patients off PD who are considered to be at increased risk for EPS (e.g. progressive ultrafiltration failure). Increased awareness of EPS due to the introduction of our EPS registry and actively informing nephrologists about the presence of possible EPS patients may have triggered Dutch nephrologists to adopt a similar policy to Japan's.

An important feature of this registry was the inclusion of suspected early cases of EPS, showing that a clinical suspicion of EPS, based on signs and symptoms of small bowel obstruction, should be taken as a serious indication for development

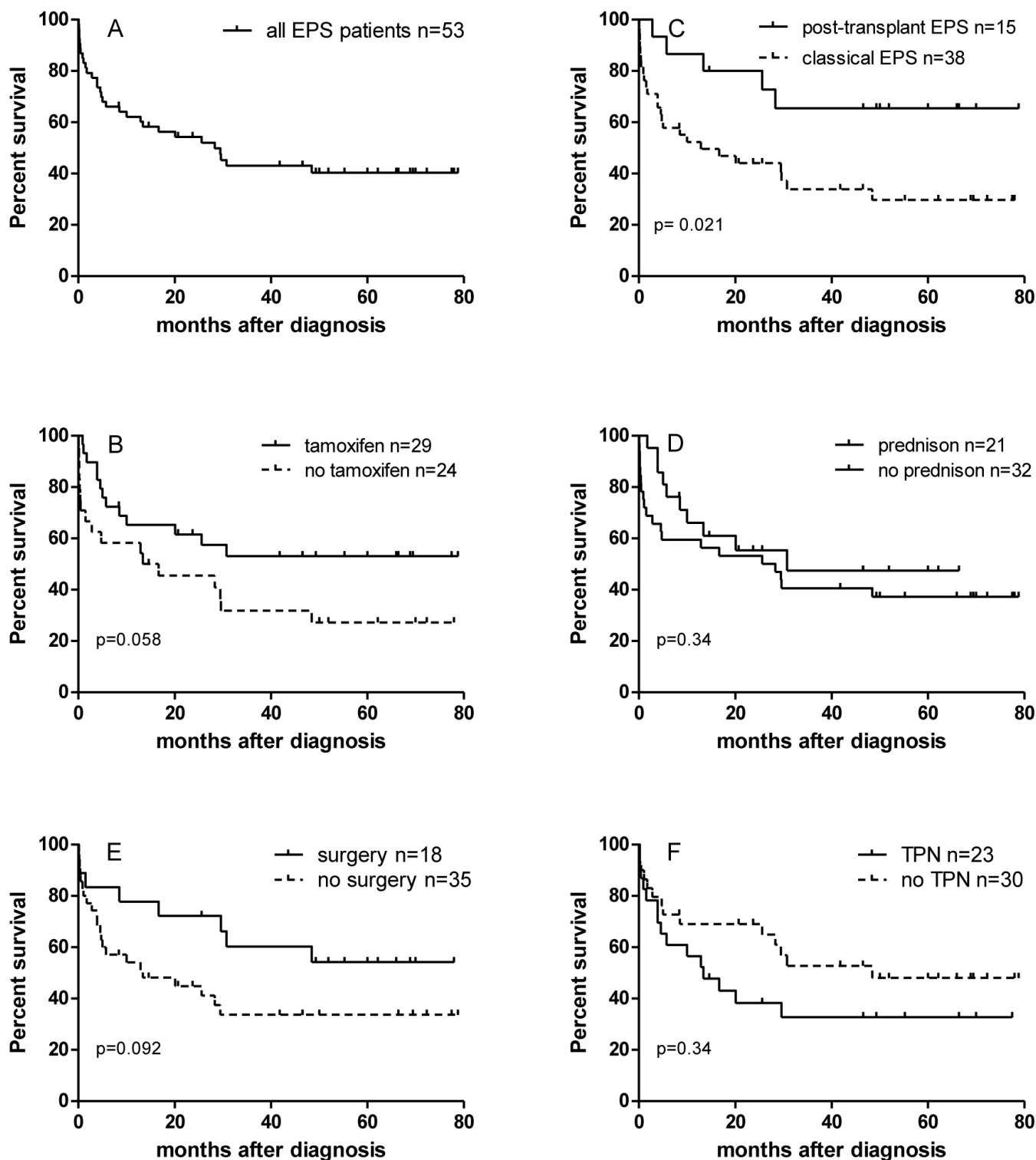


Figure 2 — The Kaplan-Meier survival curves of all registered EPS patients (A) and the subgroups of patients with classical and post-transplantation EPS (B). Survival curves for EPS patients treated with tamoxifen (C), prednisone (D), surgery (E), or TPN (F) are shown separately. The p values are obtained by log-rank test for difference between survival curves for patients groups which either did or did not receive the treatment. The number of cases within each subgroup (n) is indicated. EPS = encapsulating peritoneal sclerosis; TPN = total parenteral nutrition.

into clinical EPS. This offers the opportunity for early medical treatment with tamoxifen, for example (1,9). The lower mortality in the group of suspected early EPS may be attributed to

timely treatment with tamoxifen but may also be a reflection of less severe peritoneal sclerosis which is initially not recognized by CT scanning.

One of the strengths of the registry is the high response rate to the inquiring emails. All major medical centers likely to encounter EPS cases responded and offered their cooperation when a new patient was identified. This makes it likely that most if not all new cases of EPS in the Netherlands diagnosed after the start of the registry were included. One of the limitations of the study is that we are not able to identify why the incidence of EPS has declined in the Netherlands.

In conclusion, yearly registration of new EPS cases in the Dutch EPS Registry shows a significant decrease in the incidence of EPS over the last 3 years.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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