REVIEW

DESIGNING EPIDEMIOLOGY STUDIES TO DETERMINE THE INCIDENCE AND PREVALENCE OF ENCAPSULATING PERITONEAL SCLEROSIS (EPS)

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The reported incidence and prevalence of encapsulating peritoneal sclerosis (EPS) varies markedly between North America, Europe, Japan, and Australia. Although this could reflect differences in clinical practice patterns and access to transplantation as there is no current test for early detection, and some patients may present many years after discontinuation of peritoneal dialysis (PD), there are concerns about under-reporting, particularly for those with milder forms. Currently, only PD vintage has been identified as a significant risk factor for developing EPS, although some patients can develop EPS within months of starting PD. As such, there is a need for epidemiological studies to determine the incidence and prevalence of EPS to allow for patient education and counselling in terms of dialysis modality choice and length of treatment. In addition, carefully designed epidemiological studies could potentially allow for the identification of risk factors and bio-markers that could then be used to identify patients at increased risk of developing EPS in the future. Typically, studies to date have been underpowered with inadequate longitudinal follow-up. We review the different types of epidemiological studies and provide information as to the number of patients to be recruited and the duration of follow-up required to determine the incidence and prevalence of EPS.

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Although peritonitis carries a much greater risk of peritoneal dialysis (PD) technique failure and mortality (1), there has been much recent focus on encapsulating peritoneal sclerosis (EPS), which although relatively rare, can be a devastating complication of PD with a reported mortality varying between

32 and 75% (2,3). The pathophysiology of EPS remains to be fully elucidated. Currently, the main risk factors for developing EPS include duration of PD treatment (3,4) and probably increased exposure to higher glucose-containing dialysates as patients lose osmotic conductance (5). The reported incidence and prevalence of EPS varies markedly, with much higher rates from Japan, the UK, and The Netherlands, compared with North America and Australia (2,4,6,7). Although this variation could be due to genetic factors, it is more likely that clinical practice pattern differences, along with access to transplantation, lead to differences in duration of PD therapy, not only between centers but also between countries, and therefore almost certainly cause variation in EPS-risk between centers and countries. This is likely to introduce errors when extrapolating from overall (i.e. national) incidence rates to those for individual centers and difficulties when comparing national rates.

DEFINING THE INCIDENCE AND PREVALENCE OF EPS

Concerns have been raised about the possibility of centers both under- and over-reporting EPS cases (8). Currently there are no screening tests to detect early EPS in asymptomatic patients (6), and the diagnosis of EPS remains based on clinical suspicion confirmed primarily with radiologic findings (2). As a result, there are currently insufficient data to appropriately counsel patients with chronic kidney disease about the risk of developing EPS when choosing dialysis modality and, similarly, to decide when to stop PD in those prevalent PD patients who may be most at risk for this complication. We therefore need to reliably define the incidence and prevalence of EPS to enable large-scale epidemiological and preventive intervention studies.

QUANTIFYING EPS CASES

Suppose there is a new disease syndrome—how would an epidemiologist approach this problem? Typically, the first

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step would be to quantify how many cases there are of the new syndrome. Counting cases requires a disease definition that is accepted by all those reporting this syndrome to the authorities and researchers who investigate the disease. If a disease definition requires a particular test to confirm disease, then this test should be performed on all cases, or on a subset of cases, to allow later extrapolation. For example, in the context of influenza, it is possible to count all people who have 'flu-like symptoms' and to then test in a random subsample how many actually have influenza using polymerase chain reaction (PCR) testing and then extrapolate from the subsample that X% of people with a 'flu-like symptoms' probably have influenza. Counting cases is more challenging in the context of an asymptomatic disease, for example hypertension, as counting cases with hypertension requires systematic and standardized blood measurements in asymptomatic people in the general population. Encapsulating peritoneal sclerosis has a consensus definition based on coupling the clinical presentation with radiologic and pathologic confirmation (2), although in clinical practice, only a minority of patients have pathological confirmation. For EPS, from an epidemiological stance, the first hurdle to overcome is one of case definition, i.e. would a study only count those patients with severe symptomatic EPS, or would a study require screening of all patients who had ever been treated by PD to detect asymptomatic or mild cases of EPS? Probably a mixture of both is required, e.g. depending on symptoms, an additional screening test to confirm or refute the presence of EPS would be required. In addition, there could also be cases of PD patients who died from other causes, who may incidentally have had mild to severe EPS and who may be "missed" without

post-mortem data. Generally speaking, the choice of case definition used will lead to biases (Table 1) that need to be carefully considered in the context of each type of research study as outlined below.

DETERMINING THE POPULATION AT RISK OF EPS

Just an initial count of EPS cases is not enough—an epidemiologist would like a denominator, i.e. a measure of how many cases there are at a given point in time in a population (prevalence), or even better, how many new cases arise over a defined period of follow-up in a population (incidence). Prevalence figures and cost estimates are useful to communicate to commissioners how many people are affected by EPS at a given point in time to justify ongoing funding into research of EPS. In research studies of causation, epidemiologists prefer to use incidence because these numbers are not affected by subsequent death rates. Hence, in the context of EPS, an ideal research study would use as a denominator all people starting PD at a given center with follow-up over time, even if they switched dialysis modality or were transplanted. This requires a study in a setting in which there is continued follow-up with renal registries, as many cases of EPS are only diagnosed after modality change (7,9).

Epidemiologists can perform ecological studies designed to compare disease counts and rates between different countries, or across a range of settings, and look at variation of factors that are common in a particular country or setting. For example, it is possible to compare EPS incidence rates against the sale of particular PD dialysates in a country or center in relation to the number of prevalent PD patients. This type of study

TABLE 1
Challenges of Epidemiological Studies in the Setting of EPS

Challenge	Why does it matter?	Potential solution
Power	A study of EPS needs to be large enough to reliably detect an association with a risk factor (see Table 2)	International collaboration by all major renal registries with good routine follow-up Longer follow-up (may be unfeasible as we want to get fast answers in rapidly changing field of practice)
Absence of a uniformly applied EPS case definition	Small underpowered studies with high variability in results A high positive predictive value for an EPS case definition reduces loss in power related to non-differential misclassification	Internationally accepted case definition for what constitutes severe/mild cases Measure of how different case definitions relate to each other in terms of positive predictive value for severe cases to put historical data into context Define the clinical pathways by which EPS can be diagnosed to capture the majority of mild and severe cases
Time at risk / Follow-up	EPS doesn't just occur whilst a patient is undergoing peritoneal dialysis, but also during subsequent modalities	Follow-up systems need to be in place across modalities to detect and treat EPS (using the above definitions)

EPS = encapsulating peritoneal sclerosis.

design can be relatively inexpensive and provide important hypotheses as to potential previously unknown risk factors for EPS. Recently, there are increasing data suggesting that EPS is now more common after switching from PD to transplantation (9). So it would be interesting to review EPS rates compared with transplantation rates in different countries. The problem with ecological studies is that aggregate data are used, and that the associations of the risk factors with the disease may be very different within the individuals within countries, i.e. the data may be confounded by other factors not measured in the ecological study. In addition, a simple, reproducible case definition would need to be used across all settings. Comparing hospitalization or EPS surgery rates across healthcare settings is likely to be biased by varying thresholds for interventions. As there is currently no validated non-invasive test for diagnosing early, milder forms of EPS, most current ecological studies are likely biased (Table 2). Cross-sectional biomarker assessments in people with and without EPS may be useful to refine the case definition of EPS to aid later research studies. However, such tests may be affected by modality changes which would need to be taken into account.

IDENTIFYING RISK FACTORS FOR EPS

There are a range of epidemiologic study designs available to investigate risk factors for a particular disease or syndrome within 1 defined setting. Once the epidemiologist has counted the number of disease cases using a particular definition, the next step in identifying risk factors would be to perform a case-series or case-control study, as the data on incident cases with the syndrome are already available. A case-series study is typically used for reversible syndromes over time, in which time-varying risk factors are investigated to determine whether they coincide with disease manifestation. Given that EPS is often not reversible, a case-control study design is probably better suited as the next step in the investigation. By controls, we mean people who do not have the syndrome but are otherwise from the same source population as those in which the cases have arisen. In the context of EPS, a preferred study design for a case-control study would be a study of people with EPS, matched to patients with a similar duration of PD therapy and other potential risk factors who did not develop EPS (10). As mentioned above, if

TABLE 2
Potential Uses and Biases of Different Types of Epidemiological Study in the Setting of EPS

Type of study design	Useful for	Potential biases
Cross-sectional study	Deriving a case definition for EPS Quantifying the burden on healthcare resources	Reverse causality: For example, people with EPS have a different biomarker profile as a result of EPS
Ecological study	Understanding international variation, i.e. pinpointing potential causes that are uniform in a particular health setting and can only be detected in cross-country comparisons	Misclassification by setting: International variation may just be due to different definitions used Confounding: Exposure differences across countries are not causing differences in incidence (ecological fallacy)
Cohort study	Prospectively investigating risk factors for EPS	Selective loss to follow-up Confounding: Other risk factor not measured/investigated in the study explain study findings
Case-control study	Prospectively investigating risk factors for EPS Cheaper than cohort studies Provided controls are sampled with same length of follow-up, these can be used to calculate incidence rates If there are samples stored at start of dialysis, these can be used (will avoid problem of reverse causality)	Selection bias: For example, only including people who are currently on PD as controls, when some cases have EPS post-transplant Recall bias: For example using questionnaire data after EPS has arisen, in which cases recall their medical history with greater accuracy than controls Confounding: Reverse causality if concurrent biomarkers are used (except genetic markers)

EPS = encapsulating peritoneal sclerosis; PD = peritoneal dialysis.

the case definition for EPS relied on severe symptoms of EPS, then it is less likely that some people with EPS symptoms did not have EPS, whereas some controls may have milder asymptomatic forms of EPS. Having a high positive predictive value for EPS-compatible symptoms (i.e. the percentage of people with confirmed EPS amongst those with EPS symptoms being 90% or higher) means that misclassification of cases versus controls (those who do not have EPS-compatible symptoms) is going to lead to a more conservative but nevertheless meaningful estimate of the association between a risk factor and developing EPS. However, this approach is likely to miss milder and asymptomatic cases of EPS, and, as such, there needs to be a low threshold for suspicion and investigation of possible EPS cases. It certainly is possible to review medical records and investigate recorded risk factors amongst cases and controls, e.g. PD treatment duration (2,6,7), PD modality, dialysis prescription, use of standard or less bio-incompatible dialysates (11), transporter status (5,10), peritonitis (6,12), concomitant medications (2), age (6), and other diseases and abdominal surgeries (2) that may potentially predispose PD patients to developing EPS. However, apart from duration of PD therapy, studies have often been contradictory, particularly with relation to the role of peritonitis episodes (3,6,7,10,12). The problem with *ad hoc* case-control studies is that biomarkers as predictors of later disease cannot readily be investigated, unless these were measured or determined using stored samples at baseline before EPS developed. The reason is that biomarkers that are measured at the time of disease manifestation are likely to be influenced by the disease rather than being a risk marker. This phenomenon is called reverse causality.

DEVELOPING RISK MARKER STUDIES FOR EPS

In order to develop risk marker studies in terms of who will develop EPS over time, the only sound study design is a cohort study, in which patients on PD are recruited at baseline. Over

time, their biological samples are stored, and they have prolonged follow-up with repeat checks for development of EPS (13). Such a study would need to be large enough to detect EPS-biomarker associations. Biomarker assessments could be subsequently performed in a nested case-control design to save costs on biomarker assays. We include a table (Table 3) to show the numbers of cases and controls required in such a nested case-control study to detect standardized differences of the biomarker. For example, to detect a 0.2 increase in the standardized difference in those who will develop EPS compared with those who did not, 246 cases with EPS would be required with 4 times as many controls. This means that such a cohort study would not only need to recruit asymptomatic patients, but then follow these patients until 246 incident EPS cases were observed. Only at this stage could the investigators then unfreeze the baseline samples for these cases and for the 984 study participants who did not develop EPS over the same length of follow-up. Considering incidence rates reported by Kawanishi *et al.* (4), such a cohort study in their setting would need to recruit 12,000 patients who start PD and follow them for 8 years to obtain 246 EPS cases using their particular definition. Given the resources required for an adequately powered biomarker study, it is not surprising that most studies' reporting has been underpowered.

SUMMARY

In summary, the main difficulty in determining the incidence and prevalence of EPS is that there is no currently available reliable screening test to detect mild and asymptomatic cases, and patients may present symptomatically many years after cessation of PD (8). The diagnosis of EPS remains based on clinical suspicion confirmed primarily with radiologic findings (2). Pathologic confirmation may be obtained in those cases that come to surgery for management or for catheter removal, but, even so, there can be a marked spectrum of intra-abdominal pathology found at laparotomy

TABLE 3
Sample Sizes Required to Detect Biomarker Differences (in Terms of Biomarker Standard Deviations) with p Values of <0.05 in Case-Control Designs for a Statistical Power of 80 or 90%

Effect size ^a	Study design (case-control ratios)	Sample sizes required for 80% power with $p<0.05$	Sample sizes required for 90% power with $p<0.05$
0.1	1:1 case-control	3,142 (1,571 cases and controls)	4,206 (2,103 cases and controls)
	1:4 case-control	4,908 (982 cases, 3,926 controls)	6,570 (1,314 cases, 5,256 controls)
0.2	1:1 case-control	788 (394 cases and controls)	1,054 (527 cases and controls)
	1:4 case-control	1,229 (246 cases, 983 controls)	1,644 (329 cases, 1,315 controls)
0.3	1:1 case-control	352 (176 cases and controls)	470 (235 cases and controls)
	1:4 case-control	548 (110 cases, 438 controls)	733 (147 cases, 586 controls)
0.4	1:1 case-control	200 (100 cases and controls)	266 (133 cases and controls)
	1:4 case-control	309 (62 cases, 247 controls)	413 (83 cases, 330 controls)

^a Standardized difference of biomarker standard deviations between cases and controls.

(14). Current epidemiological studies are therefore likely to underestimate the incidence and prevalence of EPS due to the difficulty in diagnosing milder cases and the lack of a reliable screening test.

Adequately powered cohort studies with prospective biomarker measurements coupled with prolonged longitudinal follow-up are required to allow the development of screening tests. Although funding bodies may provide initial support for such studies (15), whether the necessary continued financial support required to reliably detect incident cases of EPS on long-term follow-up would be forthcoming remains to be determined.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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