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NEPHROLOGY - EDITORIAL

No need for an "expiry date" in chronic peritoneal dialysis to prevent encapsulating peritoneal sclerosis

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Encapsulating peritoneal sclerosis (EPS) is drawing attention to the PD community because of its unpredictable onset and high mortality.

Recently, the Scottish Renal Registry [1] has established the incidence of EPS and its correlation with PD duration in that region. The rate of EPS among patients on PD was 1.5%, with an incidence of 4.9 per 1,000 person-years. This rate is well within those reported previously (0.7–3.3%) [2–7]. Interestingly, the EPS rate increased with longer duration of PD up to 5 years (from 0% at <1 year to 8.8% at >5 to 6 years), and then decreased (5% at >6 years). The median duration of PD before EPS developed was 5.1 years. At the time of diagnosis only 26% of patients with EPS were on PD. In the remainder (74%), EPS was diagnosed after PD had been discontinued; 50% of them were diagnosed with EPS after kidney transplantation with calcineurin inhibitor-based immunosuppression.

An "expiry date" for PD?

In their discussion, the Scottish group asked a key question: "Should we continue PD for patients established on this treatment?". They answered this question by stating "The risk must be interpreted in context; for a patient awaiting cadaveric transplantation after several years of PD, the risk of EPS may be considered to be too great to remain on PD, whereas the same risk may be acceptable for an elderly patient with no option of transplantation".

Earlier, a group of nephrologists from The Netherlands [8], who had reported a cluster of EPS cases after kidney transplantation in patients given calcineurin inhibitors, had suggested that in patients on a waiting list for kidney transplantation PD should be stopped as soon as there are indications of ultrafiltration failure in order to prevent EPS. Furthermore, two previous publications [6, 7] also suggested that PD duration should not exceed 5 years in order to decrease the risk of EPS, irrespective of whether patients were awaiting a kidney transplant.

The concept of an "expiry date" for PD seems to be spreading among nephrologists, but we do not believe that this is an appropriate strategy for confronting EPS. This editorial will outline our reasoning in resisting such an approach.

Simple sclerosis and Encapsulating peritoneal sclerosis are separate entities: the "two hit" hypothesis

An interesting debate about the etiology and pathogenesis of EPS took place during the 1st Joint ISPD/

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EuroPD Congress in Amsterdam in 2004. In that meeting a group from Japan [9] presented evidence that in its primary pathophysiology EPS has a strong connection with simple sclerosis (SS)—the submesothelial sclerosis that is always present after years of PD—and proposed that these two conditions (SS and EPS) are but two stages of the same pathology. On the contrary a group from Italy [10] asserted that differences in frequency, pathology, animal models, etiology, and clinical impact show that EPS and SS are two separate nosological entities. We strongly feel that it is very important to understand the two conditions and their inter-relationship: if EPS is just the evolution of SS, then sooner or later all PD patients will develop EPS. Furthermore, since the bioincompatibility of PD solutions is the main etiological factor proposed to date for SS its chonic use would also be the etiology of EPS. On the contrary, if EPS is a nosological entity separate from SS, then the duration of PD is just one of the risk factors for EPS, and the true etiological factor for EPS must be a second, different stimulus leading from SS to EPS. Over the years several papers have favoured either the first [11–13] or the second view [14–16]. During the last few years, however, most nephrologists have come to accept that basically SS and EPS are two separate nosological entities, and there is a substantial agreement in considering that the pathogenesis of EPS is a "two-hit" hypothesis [17]. According to this hypothesis exposure to PD disrupts the normal peritoneal/mesothelial physiology, leading to SS, a change that can be demonstrated in any patient after a few years of PD and is probably related to the use of bioincompatible solutions. However, in a minority of patients a "second hit" is required to trigger the transition from SS to EPS. This "second hit" factor could be an episode of peritonitis or an acute intra-abdominal event, while in most patients it seems to be associated with non PD-related conditions or even with the discontinuation of PD. The link between genetic factors and EPS is also being considered, and we are looking forward to the results of the International Encapsulating Peritoneal Sclerosis Registry and DNA Bank, proposed in 2006 [18], and endorsed by the ISPD International Studies Committee [19].

Moreover, we should remember that Owtschinnikow in 1907 first described this development of EPS in non-renal patients [20], and since then the number of cases of spontaneous EPS have greatly exceeded that of the PD-related EPS [10, 14]. These non-dialytic forms may be associated with the use of β-blockers (through inhibition of surfactant release), the presence of tumors (as a paramalignant phenomenon), or may be idiopathic. The existence of these cases requires two considerations: first, they are associated with a general connective tissue abnormality, particularly of the serous membranes [21], suggesting an immune pathogenesis; second, there is a genetic predisposition, suggested by the high frequency in women from subtropical areas [22], and familial forms such as familial multifocal fibrosclerosis [23]. In a recent review, Guest [24] suggests also a possible female predominance in EPS.

No supporting evidence for an "expiry date" for long-term peritoneal dialysis

Thus we suggest that duration of PD is only one of the many risk factors for EPS but not the etiological one, and that not all PD patients are destined to develop EPS. Under these conditions, the idea of an "expiry-date" for PD seems to be an inappropriate application of the "precautionary principle". The key element of the precautionary principle is "to anticipate harm before it occurs when the absence of scientific certainty makes it difficult to predict the likelihood of harm occurring" (http://en.wikipedia.org/wiki/Precautionary_principle). In the case of PD-related EPS, the decision to discontinue PD after a pre-established period seems to be an implicit reference to this precautionary principle. Nevertheless, in biology the concept of a threshold in order to distinguish between an acceptable vs a non-acceptable consequence of a potentially harmful procedure (PD in this case) is obvious if the procedure itself is the source for the avoidable consequences, but not if the procedure is just a risk factor.

From an epidemiological point of view discontinuation of PD after a certain period would not seem to yield any significant advantage to the patient. Thus the incidence of EPS increases with the duration of PD but after about 5 years this increase seems to be lower [1–7]. The Scottish Renal Registry study [1], that produced the best published data on the association between length of PD and EPS, showed a decrease in the rate of EPS development after 6 years

of PD. Moreover, it has been established that most cases of EPS appear after the discontinuation of PD, and many consider that stopping PD may be a "second hit" that triggers the evolution to EPS. The Scottish Renal Registry [1] reported that only 26% of EPS cases are diagnosed during PD and as many as 74% appear after stopping PD, usually with an acute-onset presentation. Therefore, epidemiological data does not seem to support the concept of an "expiry date" for PD. Indeed it is possible that stopping PD at 5 years may actually increase the incidence of EPS.

Moreover, the risks of shifting patients to hemodialysis, especially with a tunnelled line, after a fixed time on PD in the absence of definite indications, could equal or even surpass the risk of ever getting EPS and could also impact negatively on the patient's quality of life [25, 26].

Exploring ways to prevent EPS

We propose that instead of postulating an expiry date for the use of PD, we should concentrate our efforts to explore ways to decrease the risk of EPS. For many years this task has been a kind of Holy Grail in peritoneal dialysis but to date we have no effective prevention of EPS. Nevertheless, data published during last few year, suggest several new possibilities.

First, the observation that 50% of EPS cases are now diagnosed in patients following transplantation, all of them in patients on calcineurin inhibitor-based immunosuppression (cyclosporine or tacrolimus) [1, 8], indicates a possible new approach to EPS prevention. The profibrotic characteristics of these drugs are well documented [27, 28]. On the contrary, mTOR inhibitors (sirolimus and everolimus) and mycophenolate mofetil do not share this negative action; in fact these immunosuppressive drugs have already been proposed as a therapy for EPS [29–31]. Moreover, to achieve a better outcome in kidney transplantation, many immunosuppressive protocols based on these drugs have been developed to prevent or to minimize the nephrotoxic effect of calcineurin inhibitors: with these new protocols most transplanted patients are managed successfully without a significant increase in rejection rate [32, 33]. Furthermore, we suggest that the current tendency to decrease or even discontinue steroids, that may prevent the development of EPS, should not be pursued rigorously in PD patients. Based on these preliminary observations, it seems reasonable to propose a study of a specialized immunosuppression protocol for PD patients receiving transplant that includes mTOR inhibitors, mycophenolate mofetil and steroids in PD patients at time of transplantation, with avoidance or minimization of calcineurin-inhibitors.

The second consideration is that while the percentage of EPS cases diagnosed after kidney transplantation is increasing as much as 50%, the percentage of cases diagnosed during PD is decreasing as much as 24% [1]. Thus, the number of EPS cases diagnosed before stopping PD seems to be decreasing [1–7]. During last few years, new biocompatible PD solutions are being used more widely and it is possible that such increased use may be responsible for a decrease in the incidence of EPS diagnosed during PD. The superior anatomical and functional biocompatibility of these solutions are well documented [34–36]. This is only an indirect indication for the widespread use of these new solutions as a means to prevent EPS, but it seems more promising than a misunderstood precautionary principle. The inhibition of renin-angiotensin system should also be considered as the elective therapy of hypertension in PD patients since a number of papers [37–39] clearly indicate a role of ACE-inhibition in preventing peritoneal fibrosis.

The third possibility concerns the patients on PD who develop ultrafiltration failure after 3–5 years. These patients are at high risk for developing EPS [1]. During the past few years, several reports [40–43] have indicated that tamoxifen is effective in EPS therapy. The results seem promising and the side effects of such therapy seem to be nearly absent, at least at low doses (10 mg per day). Tamoxifen does not carry with it the risk of infection and the difficulty in dosage adjustment that characterize steroid medication and other immunosuppressive regimens, which constitute the basis of the empirical therapy of EPS. Considering these features, one might consider low dose tamoxifen (e.g. 10 mg per day) prophylaxis of EPS in patients after 5 years of PD and/or in patients with ultrafiltration failure.

We need prospective studies of all these approaches. Both the community and industry need to undertake prospective studies for at least three years or more to better understand their potential in prevention of EPS.

For new patients requiring kidney replacement therapy, discussing their options is a complex process. The nephrologist is expected to advise his/her patients based on scientific evidence and to seriously consider all the characteristics of each individual patient; this is particularly difficult when scientific evidence is not definitely established. On the other hand, the patient should be fully informed about the risks and benefits of any kind of choice. What should be done after 5–6 years of PD should be decided by the individual nephrologist and the individual patient; nobody else has the right to judge that choice.

Conclusion

The idea of an "expiry date for PD", that is spreading among nephrologists, especially in developed countries, has no rational basis and may be potentially harmful to the patient who is forced to change to hemodialysis after a fixed time on PD in the absence of definite indications. Furthermore the risks of such a transfer, especially with a tunnelled line could equal or even surpass the risk of ever getting EPS and also could impact negatively on the patient's quality of life. We believe that instead we should concentrate our efforts on the prevention of EPS by other means. We should conduct large multi-center prospective studies in areas such as avoiding or minimizing calcineurin inhibitors in transplanted ex-PD patients, using new biocompatible PD solutions over long periods, inhibition of renin-angiotensin system, and possible prophylaxis with low-dose tamoxifen in patients on PD for a long time and/or with ultrafiltration failure.

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