Encapsulating Peritoneal Sclerosis – Comment on the 8th GPDP-SIN 2022 Census data

Census

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For many years Encapsulating Peritoneal Sclerosis (EPS) represented the greatest concern for peritoneal nephrologists, to the point of calling into question the very rationale behind peritoneal dialysis (PD). A Peter Blake editorial 14 years ago entitled “The Specter of EPS” [1] clearly described the deep unease this rare, but often fatal complication was spreading within the nephrology community, and at the same time outlined a strategy for addressing it. The first decade of the 2000s also saw an unprecedented collaboration between peritoneal nephrologists and transplanters in the Dutch experience, which documented how the EPS case incidence was higher post-transplant (Tx) than during PD [2–5]. Finally, a limited percentage of patients developing EPS following a shift from PD to hemodialysis (HD) has been documented constantly over the years [6].

In the last 10 years, several papers have reported a general reduction in the incidence of EPS diagnosed in patients on DP [7–9], whereas there is no evidence of a reduction in EPS diagnosed post-Tx or on HD.

The GPDP Censuses from 2008 to 2022 show a comforting reduction in total EPS case incidence from 0.701 episodes/100 years/patient to 0.176 episodes/100 years/patient. The same Censuses also recorded (surprisingly when compared to the international literature mentioned above) the reporting of zero cases of post-TX EPS after 2014. This comment sets out to suggest some keys to the interpretation of this trend.

As regards the reduction in the incidence of EPS in PD, the Census data are moving in the same direction as in the international literature, reinforcing the evidence: it is real. Let’s see what the reasons for this trend could be.

A recent meta-analysis [10] identified the following significantly modifiable risk factors associated with EPS in PD, in order of importance: 1) high peritoneal transport; 2) duration of the PD; 3) peritonitis.

The role of high transport clearly emerges, confirming the need to monitor the ultrafiltration and transport characteristics of every single patient regularly so as to customize the approach in the event of gradual deterioration of the parameters [11]. The GPDP Census data from 2010 to 2022 confirm that peritoneal transport is monitored by a large majority of Italian Centers; a second positive piece of data is the increasingly widespread use of 3.86%-PET vs 2.27%-PET. The close attention paid in Italian PD to this issue certainly contributes to keeping the incidence of EPS in PD low overall. We must however recognize how the minority percentage of Centers

which do not monitor transport has unfortunately increased over the course of the years: a negligible number in 2010 rose to exceed 10% in 2022. So, in the case of Italy the gradual reduction in the incidence of EPS in PD is not connected to increasingly widespread patient monitoring. It is really to be hoped that greater awareness of the importance of ultrafiltration and transport in the customization of the PD prescription and the prevention of EPS will have all Centers back assessing them regularly in the future.

The average duration of PD has remained unchanged over time (32.9 months in 2008 vs 31.6 months in 2022), so the reduction in the incidence of EPS in Italy is not correlated either with a shorter duration of PD. This is reassuring: indeed, there is general agreement on the fact that there is no PD "expiry date", and that the cost/benefits ratio clearly indicates the inadvisability of interrupting PD a priori as a preventive measure against EPS [12].

The incidence of peritonitis, on the other hand, represents the truly significant risk factor whose trend over the years genuinely correlates with the reduction in the incidence of EPS in PD: between 2005 and 2022, there was a constant reduction in the incidence of peritonitis, which substantially halved to 0.176 episodes/year/patient. It is therefore extremely likely that the brilliant results achieved in the prevention of peritonitis are the main factor that has led to the fall observed in the incidence of EPS in PD in Italy. Then again, a reduction in the incidence of peritonitis in PD has been shown throughout the world in the last decade [13] and therefore represents the main reason for the general reduction in EPS in PD.

A second factor that may have contributed to the reduction of EPS in PD is less exposure to glucose in the dialysis solutions: the Census data show an ever-increasing use over the years of incremental dialysis, from 11.9% in 2005 to 35.3% in 2022; it is clear that in periods of incremental dialysis the exposure to glucose is considerably lower than during standard PD.

Furthermore, it is widely thought (although the Census has not taken this aspect into consideration) that the use of more biocompatible dialysis solutions (icodextrin, low-GDP, amino acids) has also grown over the years. There is histological evidence of their action in preserving the structural characteristics of the peritoneum [14, 15], associated in some cases (icodextrin, amino acids) with the absence of glucose, and in others (low-GDP) with the absence of products of glucose degradation even though contained in the solution. Opinions on their greater biocompatibility vs traditional solutions are widely shared, and their use in the prevention of EPS is widely recommended [16].

With regard to post-Tx EPS, the Census data are, on the contrary, surprising. The absence of cases reported after 2014 is clearly in contrast with the international literature mentioned earlier, which in relative terms describes an ever-increasing percentage of cases of post-Tx EPS (stable over time) compared to cases of EPS in PD (falling over time).

Furthermore, while there are congruous physio-pathological explanations for the reduction in the incidence of EPS in PD (fall in peritonitis, reduction in glucose load, greater use of more biocompatible PD solutions), in the case of post-Tx EPS known physio-pathogenetic mechanisms lead to an expectation of substantial stability over time, if not an increase. It is in fact well-known that the fundamental pathogenetic mechanism in post-TX EPS is the powerful pro-fibrotic action of standard immunosuppression based on calcineurin inhibitors (CNI: tacrolimus, ciclosporin) in the absence of mTOR inhibitors (mTOR-I: sirolimus, everolimus) [17]. Over the last 10 years, on the basis of considerations that disregard EPS (effectiveness in rejection prevention, side effects on lipid metabolism) kidney transplant immunosuppressive therapy has not evolved at all towards containment of the use of CNIs in favor of mTOR-Is: the use of mTOR-Is remains marginal; as a matter of fact, tacrolimus (the most powerful CNI of all) is increasingly preferred to ciclosporin [18]. In this context, it seems that the failure to document post-Tx EPS cases can simply be interpreted as inadequacy on the part of the Census in recording them, secondary in

turn to the type of organization of the transplant system. The majority of the 40 Kidney Transplant Centers in Italy are surgically-run, and in the individual Transplant Centers (even those which are nephrology-run) there is usually no interface between the Nephrologists dealing with transplants and those responsible for PD; in some Italian Transplant Centers, the Nephrology departments do not even offer a PD service and do not concern themselves with it in the least. In the end, EPS remains a nosological entity which is fundamentally unknown to the transplant team, and is often not diagnosed at all. The likelihood of the issue being taken on by local area PD personnel (the very people the Census is necessarily aimed at!) is close to zero. In this sense, rather than an actual fall in incidence the fact that cases of post-Tx EPS were reported until 2014 and not subsequently would seem to reflect gradually more difficult working conditions, resulting in less and less contact between professionals. The distance separating the worlds of transplantation and PD can also be seen in the details: as the unit of measurement of incidence in EPS the Census has to use the number of episodes/100 years/patient, but this method – perfect for EPS in PD – is practically unusable in post-Tx EPS, where the percentage of development of post-Tx EPS should be considered in former peritoneal dialysis patients (data that can only be provided however by Transplant Centers and not by PD teams).

The organization described above is common to many countries: this is precisely why the documentation of cases of post-Tx EPS is particularly fragmentary. It is no coincidence that the only reliable statistics on post-Tx EPS are those referred to above from Holland, where there are only 2 Kidney Transplant Centers (Rotterdam and Utrecht), both of which have very well-structured Nephrology departments and PD activities: the ideal situation for establishing a fruitful, direct relationship between the worlds of PD and transplantation.

Finally, some comments on cases of EPS following a shift from PD to HD. The number of these situations has always been low, and this complicates any interpretation. However, the Census has difficulty collecting this data too, given that in many Centers the dialog between PD and HD personnel is not optimal. In this edition, as many as 50 Italian PD Centers out of 227 (22%) were unable to even transmit HD incidence and prevalence data due to their being unable to obtain the data from colleagues in their own Center. This sad reality suggests the reasonable possibility of underestimation of cases of EPS in HD, although not as generalized as in the case of post-Tx EPS. In the pathogenesis of EPS in HD the second hit responsible for the shift from simple sclerosis to EPS is represented precisely by the very interruption of PD, with suspension of the peritoneal removal of fibrin [19]. This stimulus is inevitably produced in any case at the time of the shift, so – as for post-Tx EPS – we do not even have a rationale for expecting a substantial reduction in these cases. In confirmation of this, a recent study [20] shows how a combined PD+HD therapy is associated with a reduction in the incidence of peritonitis, but not of EPS.

In conclusion, the reduction in the incidence of EPS in PD in Italy is a real phenomenon, and in keeping with data reported internationally. The main determinant is shown to be the corresponding fall in peritonitis, with the reduced glucose load and the use of more biocompatible dialysis solutions also very likely to be playing a role. The monitoring by all Centers of ultrafiltration and patient peritoneal transport characteristics is strongly to be recommended, while the incongruity of an a priori limitation of the duration of PD is confirmed.

The failure to document cases of post-Tx EPS, whose incidence is constant in international reports, seems on the other hand to be secondary to the inadequacy on the part of the Census to intercept them, which is in turn due to both a lack of Transplant Center awareness of EPS issues and the organizational separation between Transplant Centers and PD teams. A deficit in reporting is also likely with regard to EPS in HD, the rarest of all, linked to a lack of collaboration between PD and HD personnel. The take-home message is: we are achieving good results with EPS in PD, but the battle is not over yet and we have to continue to prevent, diagnose and treat it.

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