FROM THE EDITOR

Editor's introduction—genetic polymorphisms and clinical heterogeneities

A systematic review in this issue of *Peritoneal Dialysis International* (Siddique *et al.*) identifies 18 studies that examined the relationship between candidate gene polymorphisms and important outcomes for peritoneal dialysis (PD) patients, such as peritoneal membrane solute transport, peritonitis, encapsulating peritoneal sclerosis, patient and technique survival. The biological systems affected by these genetic variations include inflammatory cytokines, growth factors, and enzymes. The quality of studies varied, with the most compelling evidence of a causative role of the genetic variation coming from longitudinal studies that were able to demonstrate alterations in the concentration of a protein product or a target gene. Evidence for the role of interleukin 6 (IL-6) gene polymorphisms on peritoneal membrane small solute transport is strong and has been confirmed by the GLOBAL study (1). There is weaker evidence of associations between variations in IL-1 and peritonitis, or angiotensin-converting enzyme and vascular endothelial growth factor and patient survival. This line of investigation provides a rationale for the Biological Determinants of Peritoneal Dialysis Outcomes study funded by the US National Institutes of Health – Chief Investigator Raj Mehrotra. That study seeks to establish a genetic and bio-repository of both dialysate effluent and plasma samples to support further study of genetic determinants of baseline and longitudinal changes in peritoneal membrane function.

In contrast to polygenic influences on peritoneal membrane function, the genetics of adult autosomal dominant polycystic kidney disease (ADPKD) are much clearer, and indeed, treatments have been developed. Importantly the diagnosis is usually made from a combination of phenotype and family history, rather than relying on genetic testing. However, the role of genetic testing is set to increase since this might influence clinical decisions regarding the appropriateness of new therapeutic options (2). Because of early identification, patients with ADPKD who require dialysis are likely to have planned presentations and therefore have the best opportunity to access pre-dialysis care. This partly explains why such patients are more likely to be transplanted and have lower mortality than that associated with other causes of end-stage kidney disease. These factors are likely to have impacted on the prospective case-controlled study of 106 ADPKD patients treated with PD from 19 Spanish centers published in this issue (Janeiro *et al.*). Controls were identified from 2 consecutive non-ADPKD patients who started PD at the same center as the index case.

Thus it is unsurprising that ADPKD patients in this study had better pre-dialysis care than their case-controls, as evidenced by better anemia and blood pressure control, and experienced a higher transplant rate, as well as lower co-morbidity and less diabetes. Overall, this Spanish paper broadly confirms a paper from the French registry that PD is an entirely reasonable treatment for end-stage kidney disease due to ADPKD, in most cases while waiting for a renal transplant (3).

The Spanish study explored surgical complications of PD—finding that abdominal wall leaks were equally common in cases and controls, but were more likely to lead to transfer to hemodialysis in cases. Patients suffering from ADPKD were more likely to require nephrectomy—often as preparation for transplantation—than controls and less likely to require PD catheter repositioning. Clearly, in some cases, there are practical problems with intraperitoneal volume due to the physical presence of large native kidneys, and automated PD overnight with lower volumes during the day is appropriate while there is sufficient residual renal function. Peritoneal dialysis may no longer be appropriate for anuric patients with large native kidneys, when planned transfer to hemodialysis should be considered.

We report a pilot study in this issue (Hiramatsu *et al.*) of the impact of the vasopressin antagonist tolvaptan, at a dose of 15 mg daily, initiated 2 weeks after starting PD, in 12 diabetic patients who had evidence of volume overload compared with a historical control group. The groups were rather heterogeneous, both in terms of baseline heart failure status, diuretic, and PD prescription (for example only 10 out of the 12 received icodextrin, 9 were on automated PD). The principal results were a preservation of urine volume as well as residual creatinine and urea clearance in the tolvaptan group compared with the control. The study had design weaknesses—but certainly presents an intriguing therapeutic possibility that merits further evaluation.

Pulmonary hypertension (PH) is gaining recognition as an adverse risk factor for survival among patients on dialysis. In a prospective study of 618 incident PD patients reported in this issue of PDI (Xu *et al.*), 16% had PH defined as a pulmonary artery systolic pressure (PAP) > 35 mmHg, estimated using echocardiography. Although echocardiography can provide an estimate of PAP, the gold standard diagnostic technique is right heart catheterization, which is not practicable in a large cohort study. In this population, PH identified using echocardiography conferred an adjusted hazard ratio of 2.1 for all-cause mortality over a median follow-up period of 29 months, a similar risk to other studies in dialysis patients (4). Patients in the PH group were more likely to be diabetic, have lower serum albumin and serum sodium, have cardiovascular

disease, and they were older. The etiology of PH in the general population includes connective tissue disorders and left ventricular valvular heart disease. In dialysis patients, however, the cause is probably multifactorial, and modifiable factors are not well understood.

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