End-Stage Renal Disease in Patients with Fabry Disease

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Anderson-Fabry disease (AFD) is a rare cause of end-stage renal disease (ESRD). Renal pathology in AFD is notable for diffuse deposition of glycosphingolipid in the renal glomeruli, tubules, and vasculature. Light microscopic findings include a “foamy” appearance of the glomeruli with diffuse swelling and vacuolization of visceral podocytes. Electron microscopic findings show podocytes and mesangial cells filled with lysosomal electron dense granules arranged in a lamellar, myelin pattern. Toluidine blue stain brings out the lipid deposits in these areas. ESRD is a common complication of AFD (see Alroy et al. and Branton et al. in this issue). Current information regarding ESRD in patients with AFD derives primarily from two studies that used data from the United States Renal Data System (USRDS) and the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) registry. In this article, we review the prevalence of ESRD due to AFD, the characteristics of Fabry patients at initiation of renal replacement therapy (RRT), and the outcomes associated with dialysis and transplantation.

Prevalence of ESRD

AFD is a rare cause of ESRD. In the USRDS analysis, among 250,352 patients who began RRT in the United States between April, 1995, and July, 1998, 42 patients were identified as having ESRD due to AFD, which corresponds to 0.0167% of all causes of ESRD (1). The number of Fabry patients that began RRT in the United States in 1996, 1997, and 1998 was 12, 11, and 14, respectively (1). In the ERA-EDTA analysis of 440,665 patients who began RRT in Europe between 1987 and 1993, 83 patients were identified as having ESRD due to AFD, which corresponds to 0.0188% of all causes of ESRD (2). Although the prevalence rates reflect comparison of Fabry patients among all other patients with ESRD, the prevalence among young males who initiate dialysis before the age of 40 yr, for example, may be higher. Furthermore, there are likely additional undiagnosed AFD patients with ESRD, as not all patients undergo a renal biopsy before starting dialysis; thus the prevalence estimates above are probably underestimates.

Patient Characteristics at Initiation of RRT

Patients with AFD are younger and more likely to be male and white when compared with the overall US ESRD incident population (1). In the USRDS analysis, the mean age was 42 yr and the majority of patients began RRT between the ages of 35 and 44 yr. Despite the X-linked inheritance of AFD, 12% of patients were female and their ages ranged from 20 to 68 yr. Although AFD has been described mostly in whites, 10% of patients were African Americans and 7% were of other races.

Interestingly, Fabry patients with ESRD from the United States and Europe have many similarities, despite the geographic and potentially genetic differences between them. Although the mean age of European and US patients was 42 and 38 yr, respectively, the majority of patients in both studies began RRT between the ages of 35 and 44 yr (2). The difference in mean age in the two studies could be due to inclusion of patients younger than 15 yr in the European cohort, compared with inclusion of only adults (≥18 yr) in the US cohort. In both studies, 12% of patients were female, which supports previous observations that women’s kidneys may be severely affected (3). The basis for symptomatic disease in heterozygous females beyond lyonization and the pattern of disease expression and co-morbidities when compared with that observed in hemizygous males requires additional investigation.

Patients with AFD in the United States are more likely to have private insurance and be employed before initiation of RRT than non-Fabry controls matched by age, gender, race, year, initial ESRD treatment modality, and ESRD network (unpublished data). In the USRDS analysis, the percentage of Fabry patients with private insurance, other insurance (Medicare, Medicaid, and other), and no insurance was 64%, 22%, and 14%, respectively, and among age-matched non-Fabry patients 42%, 43%, and 15%, respectively. Six months before initiation of RRT, patients with AFD were more likely to have full-time employment compared with non-Fabry patients (48% and 42%). At the time of initiation of RRT, the patients in both groups were less likely to maintain their full-time employment (31% and 29%, Fabry versus non-Fabry) and more likely to be unemployed (22% and 27%, Fabry versus non-Fabry).

Dialysis

Fabry patients are more likely to be started on hemodialysis than on peritoneal dialysis. In the USRDS analysis of incident
ESRD patients between 1995 and 1998, the initial modality was hemodialysis in 64%, continuous ambulatory peritoneal dialysis in 22%, and continuous cycling peritoneal dialysis in 12%. Only one patient (2%) received a preemptive transplant, and two additional patients received a transplant 1 and 2 mo after an initial course of hemodialysis (1). In the ERA-EDTA analysis of incident ESRD patients between 1985 and 1993, the initial modality was hemodialysis in 78%, peritoneal dialysis in 18%, and preemptive transplantation in 1% (2).

Few studies have examined the outcomes associated with dialysis therapy among Fabry patients. Using USRDS data, the survival of 95 patients who began dialysis between 1985 and 1993 was compared with that of 256 nondiabetic and 240 diabetic controls matched by age, gender, race, year, initial ESRD treatment modality, and ESRD network. At 3 yr, survival for Fabry patients was 63% (95% confidence interval [CI], 50 to 75%), compared with 74% (95% CI, 67 to 80%) for nondiabetic controls (P = 0.03) and 53% (95% CI, 46 to 61%) for diabetic controls (P = 0.01). The survival curves for Fabry patients and nondiabetic controls began to diverge after approximately 1.5 yr. Among the Fabry patients, 42% had undergone renal transplantation by 3 yr, compared with 29% of nondiabetic and 13% of diabetic controls, suggesting our hesitation to transplant these patients has changed (see below). Data from the European registry suggests that the 3-yr survival was similar to that reported for US Fabry patients (60% versus 63%) (2). Therefore, both in the United States and in Europe, AFD patients that initiate dialysis have a worse survival compared with non-Fabry controls, even when one accounts for age. Studies on enzyme replacement therapy of AFD patients on dialysis are warranted, as this may be only hope these patients have to improve survival on dialysis.

Transplantation

Although kidney transplantation is considered the optimal therapy for ESRD in suitable patients, it is not universally accepted as the ideal treatment for patients who have suffered ESRD from AFD. There are several reasons for the historical caution with respect to kidney transplantation in AFD. First, patients with AFD are prone to premature cardiovascular and cerebrovascular events (4) (see Kampmann et al. in this issue). Second, ESRD independently confers excess risk of cardiovascular disease (CVD). Third, the cardinal risk factors for CVD—hypertension, dyslipidemia and increased adiposity commonly accompany the prolonged immunosuppressive therapy necessary for successful allograft retention in kidney transplant recipients. Thus, patients with ESRD due to AFD are considered to be at a prohibitive risk for CVD, even if offered transplantation. Nonetheless, recent estimates of rate of transplantation of Fabry patients compared with matched controls appear to be similar, suggesting this practice may be changing.

Previous published reports are conflicting with respect to the patient and allograft outcomes in AFD undergoing kidney transplantation (4–6). The majority of these studies represent small single-center experiences with limited ability to draw valid and generalizable conclusions (7–9). A recent analysis of the USRDS database found 93 incident cases ESRD due to AFD that underwent renal transplantation between 1988 and 1998 (9). A case control analysis in which kidney transplant recipients with Fabry’s were matched with controls on the basis age, race, gender, donor source (cadaveric versus living), year of transplantation, and transplant center in a 1:2 ratio (186 controls) has addressed this issue. The results suggested that approximately 25% of kidney transplant programs in the United States performed kidney transplantation in patients with AFD between 1988 and 1998. The incidence of delayed graft and acute rejection episodes were similar between cases and controls. One-, five-, and ten-year graft survival in recipients with Fabry’s (91%, 76%, and 56%, respectively) was statistically similar to the graft survival in non-Fabry’s recipients (88%, 67%, and 49%, respectively). It was further shown that the recipient survival and the risk of cardiovascular death in patients with AFD was not statistically different than that of other renal transplant recipients, with cumulative 10-yr Kaplan-Meier patient survival estimate being 67% in recipients with Fabry’s and 63% in the controls.

In contrast to the case-control study of registry data, which demonstrated equivalent outcomes in Fabry’s kidney recipients and other transplant recipients, most of the studies that reported inferior kidney transplant results in Fabry’s recipients were conducted before the widespread use of calcineurin-based immunosuppressive regimen. Notwithstanding, successful kidney transplantation in AFD has been reported by several kidney transplant programs in the United States and Western Europe (5,10). Although there are case reports of recurrence of AFD in the transplanted kidney (8) (also see Alroy et al. in this issue), it has not been shown whether disease recurrence in the endothelial cells in the allograft results in graft dysfunction or premature graft loss.

The aggregate of available data suggest that the short-term and long-term results of kidney transplantation in ESRD patients with AFD is good and comparable with that of kidney transplant recipients who developed ESRD from other causes. The excess background risk of CVD in AFD does not appear to be prohibitively exaggerated after kidney transplantation. Aggressive management of CVD risk factors before and after transplantation may be responsible for the surprisingly good patient outcomes of kidney transplantation in AFD reported above.

Summary

These recent studies of ESRD patients with AFD suggest that the risk of mortality after initiation of dialysis is significantly higher than the risk in nondiabetic controls. When these patients undergo renal transplantation, however, patient and graft survival is comparable to matched controls. Certainly there is selection bias, in that healthier patients probably undergo renal transplantation while less healthy patients may be delayed or never undergo transplantation. Nonetheless, preventing the progression of renal disease to ESRD among patients with AFD should be our main goal. If ESRD should occur, early transplantation should be our second goal. Whether enzyme replacement therapy alters outcomes while on dialysis or alters morbidity or survival (of both graft and patient) after renal transplantation has yet to be determined.
although encouraging evidence for stabilization and improvement of renal dysfunction with long-term administration of enzyme replacement has been recently reported (11).

References