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Is ERT therapy beneficial in transplant patients with Fabry disease when the diagnosis is delayed?

Editorial Comment on Sofia Santos *et al*.

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Sofia Santos *et al*. report the favourable 19-year outcome of deceased kidney transplantation in a 56-year-old male with classical Anderson-Fabry Disease (AFD), whose diagnosis was made at age 43 – i.e., 5 years after having received a kidney allograft for end-stage renal disease (ESRD) of uncertain aetiology – following the incidental observation of the typical corneal dystrophy of AFD (*cornea verticillata*) by an ophthalmologist. Enzyme replacement therapy (ERT) with agalsidase beta was eventually started at age 46. As the graft function remained stable during the long-term follow-up and there was no significant worsening neither of the left ventricular hypertrophy, as assessed by echocardiography, nor of the cerebral small vessel disease on magnetic resonance brain imaging over the 10 years of treatment with agalsidase beta, the authors concluded that ERT is safe and effective treatment for the extrarenal manifestations of AFD in kidney transplant patients.

In the pre-ERT era, analysis of kidney transplant outcomes in patients diagnosed with AFD, identified through the United States (US) Renal Data System Registry database, showed equivalent graft and patient survival rates in AFD and case-matched non-AFD patients[1]. In 2009, using data from the US Organ Procurement Transplant Network / United Network for Organ Sharing, Shah *et al*. reported the outcomes of kidney transplantation in the 197 AFD patients who had received a kidney allograft between 1987 and 2007, but did not specify how many of them had also received ERT and for how long. The 5-year graft survivals were similar in patients with or without AFD, but AFD conferred a higher risk of death as compared to matched controls with other causes of ESRD[2]. Unfortunately, these studies reported only retrospective data on graft and patient survival and did not look at the efficacy of ERT, particularly on the outcomes of the graft function and the progression of extrarenal AFD involvement. Indeed, no randomised controlled trial has ever been performed to assess the progression of cardiomyopathy in ERT-treated and ERT-untreated AFD kidney transplant patients.

So far, the lengthiest collaborative open label study of the efficacy of ERT in kidney transplant recipients with AFD was conducted in Italy, where the relevant clinical data from 17 patients on ERT either with agalsidase alfa or agalsidase beta, who had received a kidney allograft, were prospectively collected over a long-term follow-up period. After a 48-month course of ERT, mean serum creatinine had increased non-significantly from 1.78 mg/dl at baseline to 1.92 mg/dl, with a rate of decline in renal function of -1.92 ml/min/year, as estimated by creatinine clearance. No significant change in AFD-related cardiomyopathy was noted at the study completion, while the incidence of severe cardiac and cerebrovascular events was very low. The outcomes of 16 ERT-treated AFD patients on chronic dialysis were simultaneously analysed: in this cohort; the incidence of life-threatening events was significantly higher than in transplant patients, and the overall mortality due to cardiac and cerebrovascular complications was high[3]. Similar results were observed by Cybulla *et al.*, who examined the efficacy of the treatment with agalsidase alfa in 20 kidney transplant patients enrolled in the Fabry Outcome Survey registry, and reported non-significant variations in serum creatinine (1.6 mg/dl *versus* at 1.4 mg/dl at baseline) and glomerular filtration rate estimated from serum creatinine (51.1 ml/min/1.73 m^2 *versus* 59.2 ml/min/1.73 m^2 at baseline), after two years of ERT[4].

The results of these studies seem to demonstrate that agalsidase treatment of AFD kidney transplant recipients is safe and effective in stabilizing graft function, and additionally appears to limit the incidence of severe AFD-related complications as compared to ERT--treated patients remaining on dialysis. However, earlier studies – i.e., reported in the pre-ERT era – documented good graft and patient survivals also in AFD kidney transplant patients who did not receive ERT[1]. Although it can be argued that ERT stabilizes the AFD-related cardiomyopathy in kidney transplant recipients[3,5], the supporting evidence is not compelling and more studies addressing the course of cardiomyopathy after kidney transplantation, both in ERT-treated or untreated AFD patients, are clearly needed, with the same holding true also for AFD-related cerebrovascular disease.

The recently published European Best Practice Guideline on Fabry nephropathy[6] did not advocate ERT for renal indications after kidney transplantation, but suggested that it might be continued for non-renal indications[6]. Perhaps these guidelines are too conservative and ambiguous, and the following arguments in favour of prescribing ERT for every AFD patient receiving a kidney allograft might be put forward: (*i*) ERT was shown to improve extrarenal AFD symptoms, such as the painful acroparesthesias, and to reduce the incidence of severe cardiovascular events in kidney transplant patients[3,7]; (*ii*) cardiovascular disease is a major cause of morbidity and mortality in kidney transplant recipients, irrespective of the underlying aetiology of ESRD[8]; (*iii*) most, if not all, AFD patients who eventually receive a kidney allograft will exhibit extrarenal manifestations of the disease.

The case reported by Santos *et al*. is representative of the clinical course that many patients with classical AFD – as well as with other rare kidney disorders – have experienced: the diagnosis is often delayed for many years after the initial clinical manifestations, and eventually established only when the progressive storage of globotriaosylceramide and related compounds has already caused irreversible tissue damage and organ failure. Screening studies carried out among patients on renal replacement therapies have documented that the prevalence of the AFD disease was 10-fold higher than previously estimated by questionnaires[9], showing that many classically affected AFD patients may remain undiagnosed even in advanced disease stages. In addition to the late diagnosis, initiation of ERT in this patient was delayed for about three years more, when he already presented unequivocal electrocardiographic and echocardiographic evidence of heart disease progression. The limited efficacy of ERT when started late in the course of AFD[10] should be a compelling argument for early institution.

Santos *et al*. concluded that ERT was effective for the treatment of the extrarenal AFD manifestations in their patient. However, the new onset of sensorineural hearing loss, needing cochlear hearing implants, and of severe arrhythmia, leading to the indication for permanent cardiac pacing, respectively 4 and 9 years after starting treatment with agalsidase beta, should be viewed as evidence of AFD progression, and temper a too-optimistic conclusion about the efficacy of ERT in this patient.

Major teaching points of this case report are that the diagnosis of classic AFD is frequently overlooked at the early stages, and that nephrologists should be aware of Fabry nephropathy in the differential diagnosis of proteinuric chronic kidney disease, particularly in young adult males, in order to avoid unjustifiable and potentially detrimental delays in the prescription of specific therapy.

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