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Rapid Multisystem Deterioration After Enzyme Replacement Therapy Discontinuation in Fabry Disease: A Familial Case Series with Kidney Transplantation

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To the Editor,

Fabry disease (FD) is an X-linked lysosomal storage disorder with progressive kidney cardiac, and neurological involvement. Enzyme replacement therapy (ERT) remains the cornerstone of management; however, the clinical consequences of treatment discontinuation are not well defined.[1,2]

A 35-year-old male patient with genetically confirmed FD carrying the hemizygous GLA variant c.126G>A (p.Met42Ile) was evaluated. At the time of diagnosis at 29 years of age, he had stage 2 chronic kidney disease and was initiated on ERT with agalsidase beta at an external center. The patient remained compliant with treatment for approximately 3 years. However, at the age of 32 years, he voluntarily discontinued ERT, and was subsequently lost to follow-up for the next 3 years. Written informed consent was obtained from the patient who agreed to take part in the study.

The patient later presented to our center with clinical findings consistent with end-stage kidney disease. During hospitalization, maintenance hemodialysis was initiated. Comprehensive evaluation revealed advanced multisystem involvement, including marked left ventricular hypertrophy on echocardiography and central nervous system involvement characterized by white matter lesions on brain magnetic resonance imaging. During follow-up, the patient developed status epilepticus requiring admission to the intensive care unit.

Following stabilization, he was discharged on a thrice-weekly hemodialysis program, and ERT with agalsidase beta was reinitiated at a standard dose of 1 mg/kg every 2 weeks. After 4 months of regular treatment and clinical follow-up, family screening was performed. His father, who had no evidence of FD, was subsequently deemed suitable as a living kidney donor. The patient successfully underwent living-donor kidney transplantation, achieving stable graft function under standard immunosuppressive therapy. Enzyme replacement therapy was continued after transplantation as part of his long-term disease management strategy.

Cascade family screening identified 2 additional affected individuals: a 7-year-old asymptomatic heterozygous daughter and an 18-year-old sister with mild acroparesthesia but no evidence of organ involvement. Both were enrolled in regular follow-up programs.

This case highlights 3 important clinical implications. First, discontinuation of ERT may lead to rapid and potentially irreversible multisystem progression, even in previously treated patients.[1,2] Second, while kidney transplantation is an effective option for advanced Fabry nephropathy, it does not correct the underlying metabolic defect, and extra-renal manifestations may continue to progress without ongoing disease-specific

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therapy.[3] Third, cascade family screening remains essential for early diagnosis and timely intervention in hereditary diseases such as FD.[4]

In conclusion, uninterrupted ERT is critical in FD management, and clinicians should strongly emphasize treatment adherence. Early identification of affected family members through systematic screening may significantly improve long-term outcomes.

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