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Variable clinical features of patients with Fabry disease and outcome of enzyme replacement therapy

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Fabry disease (FD) is an X-linked lysosomal disorder caused by a deficiency in the enzyme alpha-galactosidase A due to mutations in the α-galactosidase A (*GLA*) gene (OMIM 301500, RefSeq NM_000169.2). This leads to an accumulation of globotriaosylceramide (GL-3) in many tissues, which results in progressive damage to the kidneys, heart, and nervous system. We present the molecular and clinical characteristics of 24 adults and two children with FD from a multidisciplinary clinic at the University of California, Irvine. We describe two novel variants not previously reported in the literature in patients with features of classic FD. The vast majority of patients in this cohort present with symptoms of classic FD including peripheral neuropathic pain, some form of cardiac involvement, angiokeratomas, corneal verticillata, hypohidrosis, tinnitus, and gastrointestinal symptoms, primarily abdominal pain. The majority have renal involvement, with the most common presentation being proteinuria, and one individual required a renal transplant. Other common findings were pulmonary involvement, lymphedema, hearing loss, and significantly, three patients had strokes. Notably, there was a high incidence of endocrine dysfunction and low bone mineral density, several of whom have osteoporosis. While enzyme replacement therapy (ERT) cleared plasma GL-3 in this cohort, there was limited improvement in renal function or health-related quality of life based on the patient-reported SF-36 Health Survey. Physical functioning significantly declined over the course of ERT treatment, which may be, in part, due to the late initiation of ERT in several patients. Further delineation of the phenotypic and genotypic spectrum in patients with FD and the long-term outcome of ERT will help improve management and treatment options for this disease.

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