Case Report

Early initiation of enzyme replacement therapy in classical Fabry disease normalizes biomarkers in clinically asymptomatic pediatric patients

Amy Kritzer\textsuperscript{a}, Aishwarya Siddhartha\textsuperscript{a}, Kate Leestma\textsuperscript{a}, Olaf Bodamer\textsuperscript{a,b,*}

\textsuperscript{a} Division of Genetics and Genomics, Department of Pediatrics, Boston Children’s Hospital, Boston, MA, United States of America
\textsuperscript{b} Broad Institute of Harvard University and MIT, Cambridge, MA, United States of America

\textbf{ABSTRACT}

Fabry disease is an X-linked lysosomal storage disorder which often presents with renal, cardiac, gastrointestinal, and nervous system abnormalities. Available enzyme replacement therapies have demonstrated efficacy at significantly reducing elevated biomarkers associated with increased disease activity, while improving the clinical symptoms associated with Fabry disease. In two cases with classical Fabry disease, we demonstrate that the initiation of enzyme replacement therapy prior to the onset of overt clinical disease is well tolerated and effectively reduces elevated biomarkers, mitigating unnecessary organ damage that may occur prior to the onset of clinical manifestations of disease. This proactive approach should be considered as a best-practice management strategy which has the potential to significantly improve health outcomes in patients with classical Fabry patients, particularly in the context of newborn screening for Fabry disease.

\textbf{1. Introduction}

Fabry disease (FD) is a rare, X-linked lysosomal storage disease due to hemizygous or heterozygous, pathogenic variants in the \textit{GLA} gene. Variable deficiency of the enzyme \( \alpha \)-galactosidase results in progressive accumulation of complex lipids including globotriaosylceramide (Gb3) and its derivative globotriosylsphingosine (lyso Gb3) in selected tissues, which may already start prenatally \cite{1,2,3}. Affected individuals with classical FD may experience multi-systemic disease that typically involves the renal, cardiac, pulmonary and nervous systems although severity and extent of involvement vary by age, gender, genotype and yet to be identified genetic modifier. Most pathogenic \textit{GLA} mutations are private and non-recurrent, making phenotype-genotype correlations difficult especially in light of significant intrafamilial variability.

In males with classical FD, clinical symptoms may first manifest during childhood including acroparesthesias (neuropathic pain), autonomic dysfunction, hypohydrosis, angiokeratomas, and gastrointestinal complaints such as diarrhea and abdominal pain. Proteinuria may be an early sign of renal involvement. Disease progression into adulthood will significantly increase the risk for cerebrovascular complications including stroke, cardiomyopathy and/or end stage renal disease. Although the exact pathogenesis of FD is still under investigation, the accumulation of Gb3 and lyso Gb3 in vascular endothelia and subsequent inflammation is thought to play a significant role \cite{2,3,4,5}.

Intravenous recombinant enzyme replacement therapy (ERT) for the treatment of FD has been first licensed in the US in 2001. ERT has been shown to improve the clinical symptoms of FD \cite{6,7,8}. It significantly reduces plasma Gb3 and lyso Gb3 levels, and Gb3 as well as lyso Gb3 storage in the myocardium, kidneys, and skin. ERT stabilizes renal function if initiated in patients with urinary protein excretion < 1 g/24 h and slows progression of renal insufficiency in those patients with significant proteinuria, improves pulmonary and gastrointestinal symptoms, and reduces the risk for renal, cardiac, and CNS events underscoring the importance of timely initiation of treatment, ideally at a pre-symptomatic stage \cite{6,7,8}.

With the advent of newborn screening for Fabry Disease, the number of asymptomatic newborn infants with FD will drastically increase \cite{9}. Limited genotype-phenotype correlation and the large number of mostly private \textit{GLA} mutations makes the prediction of disease severity and the timing of appropriate ERT initiation nearly impossible \cite{10}. The initiation of ERT subsequent to the presentation of first signs of disease (e.g. proteinuria) disregards evidence that irreversible organ damage may have already occurred \cite{10}.

Here we report two male patients with molecularly confirmed, predicted classical FD who were started on ERT at ages 3 and 5 respectively and who showed sustained normalization of previously elevated biomarkers within one year of treatment.

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*Corresponding author at: Division of Genetics and Genomics, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, United States of America.
E-mail address: olaf.bodamer@childrens.harvard.edu (O. Bodamer).

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2. Case 1

The first proband is a now 6-year-old clinically asymptomatic boy with classical FD. He was first diagnosed at the age of 6 months after targeted testing of a known familial pathogenic GLA variant, I317T (c.10658 T > C). This variant has been reported to result in classical targeted testing of a known familial pathogenic signiﬁcant for acroparesthesias, hypohidrosis and stroke in his maternal grandfather. His mother is clinically asymptomatic but has mild microalbuminuria (urine microalbumin 45 μg/mg creatinine) and increased urine Gb3 excretion (30 μg/mmol creatinine; reference range < 0.2). Percutaneous needle biopsy of her kidney showed extensive vacuolization of all glomeruli on light microscopy and presence of lamellated bodies in podocytes on electron microscopy which prompted initiation of ERT q2weeks. The proband carries a known pathogenic familial variant in GLA r.195_546dup352:800_801ins217 GenBank X14448:g10293_10509, 195_546dup352).

The proband was evaluated for FD related organ complications, including renal disease. All tests including renal and cardiac evaluations were found to be within normal limits for his chronological age. Plasma Gb3 levels at baseline were 35 ng/mL (normal < 5 ng/mL, Sanofi Genzyme Inc.). The marked elevation of plasma Gb3 levels as a reflection of disease burden and the predicted classical FD phenotype led us to initiate intravenous ERT with algalsidase-beta at 1 mg/kg q2weeks at 5 years and 3 months of age. Lyso Gb3 levels decreased to 5.1 ng/mL after 4 months of ERT and normalized after 8 months of ERT (normal < 5 ng/mL, Sanofi Genzyme Inc.). Algalsidase-beta IgG antibodies have been monitored at regular intervals and continue to be negative.

3. Case 2

The second proband is a now 4-year-old boy with classical FD, as well as a diagnosis of hemophilia A. He was diagnosed with FD at the age of 2 years and 1 month following absent alpha-galactosidase activity of 0.2 nmol/h/mg (normal ≥ 23.1). His family history is signficant for acroparesthesias, hypohidrosis and stroke in his maternal grandfather. His mother is clinically asymptomatic but has mild microalbuminuria (urine microalbumin 45 μg/mg creatinine) and increased urine Gb3 excretion (30 μg/mmol creatinine; reference range < 0.2). Percutaneous needle biopsy of her kidney showed extensive vacuolization of all glomeruli on light microscopy and presence of lamellated bodies in podocytes on electron microscopy which prompted initiation of ERT q2weeks. The proband carries a known pathogenic familial variant in GLA r.195_546dup352:800_801ins217 GenBank X14448:g10293_10509, 195_546dup352).

The proband was evaluated for FD related organ complications, including renal disease, which were found to be within normal limits for the child’s age. He had a normal urinalysis including urine beta-2 micro-globulin and albumin. Urine Gb3 excretion was markedly increased (1197 μg/mmol creatinine; reference range: 13–300). Plasma lyso Gb3 level at the time of ERT initiation was 52.2 ng/mL (normal < 5 ng/mL, Sanofi Genzyme Inc.). The more than tenfold elevation of plasma lyso Gb3 levels as a reflection of disease burden and the predicted severe classical FD phenotype led us to initiate intravenous ERT with algalsidase-beta at 1 mg/kg q2weeks at 3 years and 6 months of age. Lyso Gb3 levels normalized after 10 months of ERT to below the level of quantification (  9.20,21]. Our cases illustrate that treatment is well-tolerated in young children and can quickly normalize biomarkers, thus underscoring the potential that early treatment has to decrease overall disease burden and minimize previously reported impacts on psychosocial functioning. Although ERT requires biweekly infusions, the beneﬁts of therapy both to health outcomes and psychosocial functioning of affected patients and their families supports early, pre-symptomatic treatment as the best current management strategy.

Declaration of Competing Interest

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