Molecular Genetics and Metabolism Reports 21 (2019) 100530

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Case Report

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

Amy Kritzer[a], Aishwarya Siddharth[a], Kate Leestma[a], Olaf Bodamer[a,b,*]

[a] Division of Genetics and Genomics, Department of Pediatrics, Boston Children's Hospital, Boston, MA, United States of America
[b] Broad Institute of Harvard University and MIT, Cambridge, MA, United States of America

ARTICLE INFO

Keywords:
Fabry disease
Enzyme replacement
Globotriaosylceramide
Pediatric

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.

1. Introduction

Fabry disease (FD) is a rare, X-linked lysosomal storage disease due to hemizygous or heterozygous, pathogenic variants in the *GLA* gene. Variable deficiency of the enzyme α-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 [1–3]. 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 *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 [2,4,5].

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 [6–8]. 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 [6–8].

With the advent of newborn screening for Fabry Disease, the number of asymptomatic newborn infants with FD will drastically increase [9]. Limited genotype-phenotype correlation and the large number of mostly private *GLA* mutations makes the prediction of disease severity and the timing of appropriate ERT initiation nearly impossible [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 [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.

* 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).

https://doi.org/10.1016/j.ymgmr.2019.100530
Received 2 October 2019; Accepted 3 October 2019
Available online 19 October 2019

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 Fabry disease [11]. At the time of diagnosis he was asymptomatic on physical exam and per history. His urinalysis was within normal limits including urine beta-2 micro-globulin and albumin. His family history is significant for a maternal uncle who presented with hearing loss and end stage renal disease at 34 years of age. He was started on ERT following renal transplantation. Fifteen years post-transplant he continues to have renal function within normal limits while he continues on ERT. A second, affected maternal uncle had a stroke at 56 years of age without known risk factors for cardiovascular disease. He was on ERT for 7 years and died at the age of 63 following a second stroke. The maternal grandmother has been clinically asymptomatic per report although details are not available. She has been treated with ERT for about one year in the past, but decided to discontinue ERT since. The proband's mother is currently in her 30s and has a history of intermittent tingling in her feet since adolescence, but is currently not on ERT.

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 lyso Gb3 levels at baseline were 35 ng/mL (normal < 5 ng/mL, Sanofi Genzyme Inc.). The marked elevation of plasma lyso 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 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_546dupl352;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 (< 5 ng/mL). Algalsidase-beta IgG antibodies remain within normal limits.

4. Discussion

Progressive accumulation of complex lipids including Gb3 and lyso Gb3 in tissues occurs prior to the onset of clinical symptoms in mid-childhood [12,13]. Plasma and dried blood spot Gb3 and lyso Gb3 levels are a direct reflection of their tissue accumulation and an approximation of disease burden. It is yet unclear whether there is a critical threshold that justifies initiation of ERT. Interpretation of dried blood spot Gb3 and lyso Gb3 levels need to take into account that they are.

A recent trial has demonstrated cellular and vascular injury in the kidneys in the majority of treatment naïve, oligosymptomatic males aged 5–18 years with classical FD [14] This study underscores the pre-symptomatic onset of disease pathology in males with classical FD and elevated plasma Gb3 levels [14]. The accumulating glycolipids Gb3 and lyso Gb3 in FD trigger a cellular inflammatory and apoptotic responses through direct interaction with toll-like receptors [15]. The inflammatory response may vary between tissues, depending on the presence or absence of exolysosomes. Accumulation of lyso Gb3 particularly in renal tissues leads to excretion of pro-inflammatory and pro-fibrotic cytokines that in addition to cellular inflammation results in tissue fibrosis and impairment of renal function [15].

The psychosocial impact of Fabry disease on children, adolescents and adults has previously been well documented [16,17]. Psychosocial difficulties for children with FD may include frequent school absences, poor participation in physical activity, and behavioral problems mostly related to chronic pain and GI symptoms. One study indicated that 80.9% of patients with FD responded that it has negatively impacted their ability to attend school and 83% of patients indicated that FD had affected their ability to participate in sports and physical activities [4,17]. Pediatric patients with FD reported significantly lower Quality of Life (QoL) scores compared to healthy controls across the domains of physical health, school functioning and social functioning [16,19]. These QoL scores were comparable to patients in oncology and rheumatology cohorts. When comparing pediatric patients on ERT with those not on ERT, the ERT group reported significantly lower attention problems and higher adaptive skill functioning. Additionally, parents of children in the ERT group reported lower mean depression scores in their children [16,17,19,20]. This is an important observation, as high rates of adults with FD experience depressive symptoms [18].

Early diagnosis of FD and timely initiation of ERT provides an opportunity to improve clinical outcomes and avoid disease related long-term complications. Our cases demonstrate that early treatment with ERT, years before presumed symptom onset, can reduce lyso Gb3 levels below detectable limits. ERT is typically well-tolerated and has the potential to prevent significant, multi-system disease and greatly enhance health outcomes. Early treatment also has the potential to enhance QoL, including cognitive, social and developmental health. With the addition of Fabry disease to newborn screening protocols, increasing numbers of patients will be identified at an earlier asymptomatic stage of disease. This has raised important questions about the optimal time to begin treatment [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

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Amy Kritzer and Olaf Bodamer have received research support,

honoraria and travel support from Sanofi Genzyme, Cambridge, MA, United States of America.

References

[1] A. Mehta, D.A. Hughes, Fabry disease, in: M.P. Adam (Ed.), GeneReviews®, University of Washington, Seattle, 1993.
[2] C. Wanner, et al., European expert consensus statement on therapeutic goals in Fabry disease, Mol. Genet. Metab. 124 (2018) 189–203.
[3] D.P. Germain, Fabry disease, Orphanet J. Rare Dis. 5 (2010) 30.
[4] K.D. MacDermot, A. Holmes, A.H. Miners, Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males, J. Med. Genet. 38 (2001) 750–760.
[5] A. Tuttolomondo, et al., Anderson-Fabry disease: a multiorgan disease, Curr. Pharm. Des. 19 (2013) 5974–5996.
[6] G. De Schoenmakere, D. Chauveau, J.-P. Grünfeld, Enzyme replacement therapy in Anderson-Fabry's disease: beneficial clinical effect on vital organ function, Nephrol. Dial. Transplant. 18 (2003) 33–35.
[7] G. Bierer, D. Balfe, W.R. Wilcox, Z. Mosenifar, Improvement in serial cardiopulmonary exercise testing following enzyme replacement therapy in Fabry disease, J. Inherit. Metab. Dis. 29 (2006) 572–579.
[8] M. Arends, et al., Retrospective study of long-term outcomes of enzyme replacement therapy in Fabry disease: analysis of prognostic factors, PLoS One 12 (2017) e0182379.
[9] W.P. Wasserstein, et al., The New York pilot newborn screening program for lysosomal storage diseases: report of the first 65,000 infants, Genet. Med 21 (2019) 631–640.
[10] R.Y. Wang, O.A. Bodamer, M.S. Watson, W.R. Wilcox, ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases, Lysosomal storage diseases: diagnostic confirmation and management of presymptomatic individuals, Genet. Med 13 (2011) 457–484.
[11] J. Shabbeer, M. Yasuda, E. Luca, R.J. Desnick, Fabry disease: 45 novel mutations in the alpha-galactosidase a gene causing the classical phenotype, Mol. Genet. Metab. 76 (2002) 23–30.
[12] C. Tøndel, et al., Foot process effacement is an early marker of nephropathy in young classic Fabry patients without albuminuria, Nephron 129 (2015) 16–21.
[13] F. Perretta, N. Antongiovanni, S. Jaurretche, Early renal involvement in a girl with classic Fabry disease, Case. Rep. Nephrol. 2017 (2017) 9543079.
[14] F.A. Wijburg, et al., Characterization of early disease status in treatment-naive male paediatric patients with Fabry disease enrolled in a randomized clinical trial, PLoS One 10 (2015) e0124987.
[15] P. Rozenfeld, S. Feriozzi, Contribution of inflammatory pathways to Fabry disease pathogenesis, Mol. Genet. Metab. 122 (2017) 19–27.
[16] N. Bugescu, et al., The psychosocial impact of Fabry disease on pediatric patients, J. Pediatr. Genet. 5 (2016) 141–149.
[17] L. Sigmundsdottir, et al., Cognitive and psychological functioning in Fabry disease, Arch. Clin. Neuropsychol. 29 (2014) 642–650.
[18] A.L. Cole, et al., Depression in adults with Fabry disease: a common and underdiagnosed problem, J. Inherit. Metab. Dis. 30 (2007) 943–951.
[19] N. Bugescu, A. Alioto, S. Segal, M. Cordova, W. Packman, The neurocognitive impact of Fabry disease on pediatric patients, Am. J. Med. Genet. Part B Neuropsychiatr. Genet 168B (2015) 204–210.
[20] R.J. Hopkin, et al., The management and treatment of children with Fabry disease: a United States-based perspective, Mol. Genet. Metab. 117 (2016) 104–113.
[21] T.-R. Hsu, D.-M. Niu, Fabry disease: review and experience during newborn screening, Trends. Cardiovasc. Med. 28 (2018) 274–281.