Pregnancy Outcome After Exposure to Migalastat: A Case Study

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INTRODUCTION

- Fabry disease is a rare X-linked lysosomal storage disorder caused by deficiency of α-galactosidase A (α-Gal A), encoded by the *GLA* gene[1]
- The resulting accumulation of globotriaosylceramide (GL-3) produces a wide variety of debilitating signs and symptoms, including cardiomyopathy, renal failure, cerebrovascular events, and gastrointestinal manifestations[2]
- The first clinical symptoms of Fabry disease typically occur during childhood, and, if left untreated, the burden of disease increases over time[3]
- Until recently, enzyme replacement therapy (ERT), consisting of infusions of agalsidase alfa or agalsidase beta, was the standard treatment approach for patients with Fabry disease[4]
- Migalastat is a small-molecule pharmacological chaperone designed to bind selectively and reversibly to the active sites of *amenable* mutant forms of α-Gal A[5,6]
  - It is estimated that approximately 35-50% of Fabry patients worldwide have amenable mutations[5]
  - Migalastat binding stabilizes the mutant forms of α-Gal A and facilitates their proper trafficking to lysosomes, where dissociation of migalastat then restores endogenous α-Gal A activity, leading to the catabolism of GL-3 and other disease substrates[6]
- In the phase 3 FACETS (NCT00925301) and ATTRACT (NCT01218659) trials, migalastat was shown to provide clinical benefits for patients with Fabry disease and amenable mutations and was generally well tolerated[7,8]
- Migalastat is now approved for long-term treatment of Fabry disease in patients ≥16 years old in the European Union, Switzerland, Israel, Australia, and Republic of Korea and in adult patients in Canada[6]
- In rabbits, developmental toxicity was observed at maternally toxic doses[6]
  - As a result, migalastat is not recommended during pregnancy

OBJECTIVE AND METHODS

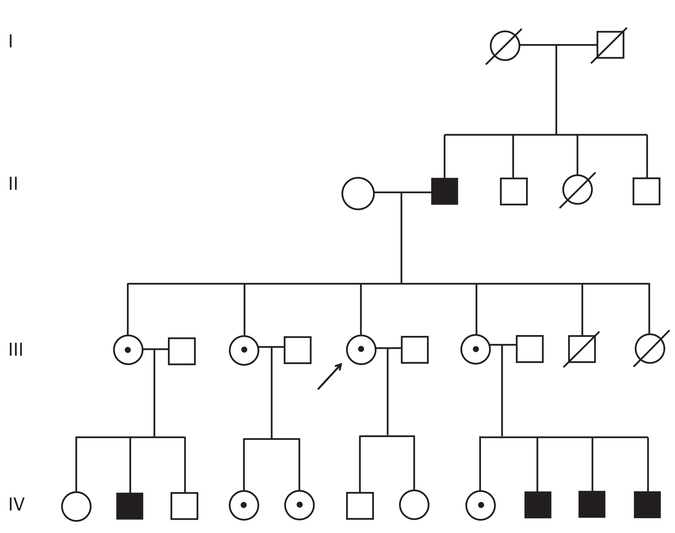
- To describe the medical history and outcome of a Caucasian woman with Fabry disease who became pregnant, despite hormonal contraceptives, while being treated with migalastat during the phase 3 ATTRACT trial
- The 18-month, randomized, active-controlled study aimed to assess the effects of migalastat on renal function in patients with Fabry disease previously treated with ERT[8]
- Patients of reproductive potential agreed to use medically accepted methods of contraception throughout the duration of the study and for up to 30 days after the last dose of migalastat

CASE REPORT

Patient History

- The patient was a Caucasian woman with Fabry disease aged 35 years at the time of migalastat initiation and 37 years at the time of pregnancy
- Her family history is shown in **Figure 1**
  - Her father was had Fabry disease (generation II), and all 3 surviving siblings (all females) also have Fabry disease (generation III)

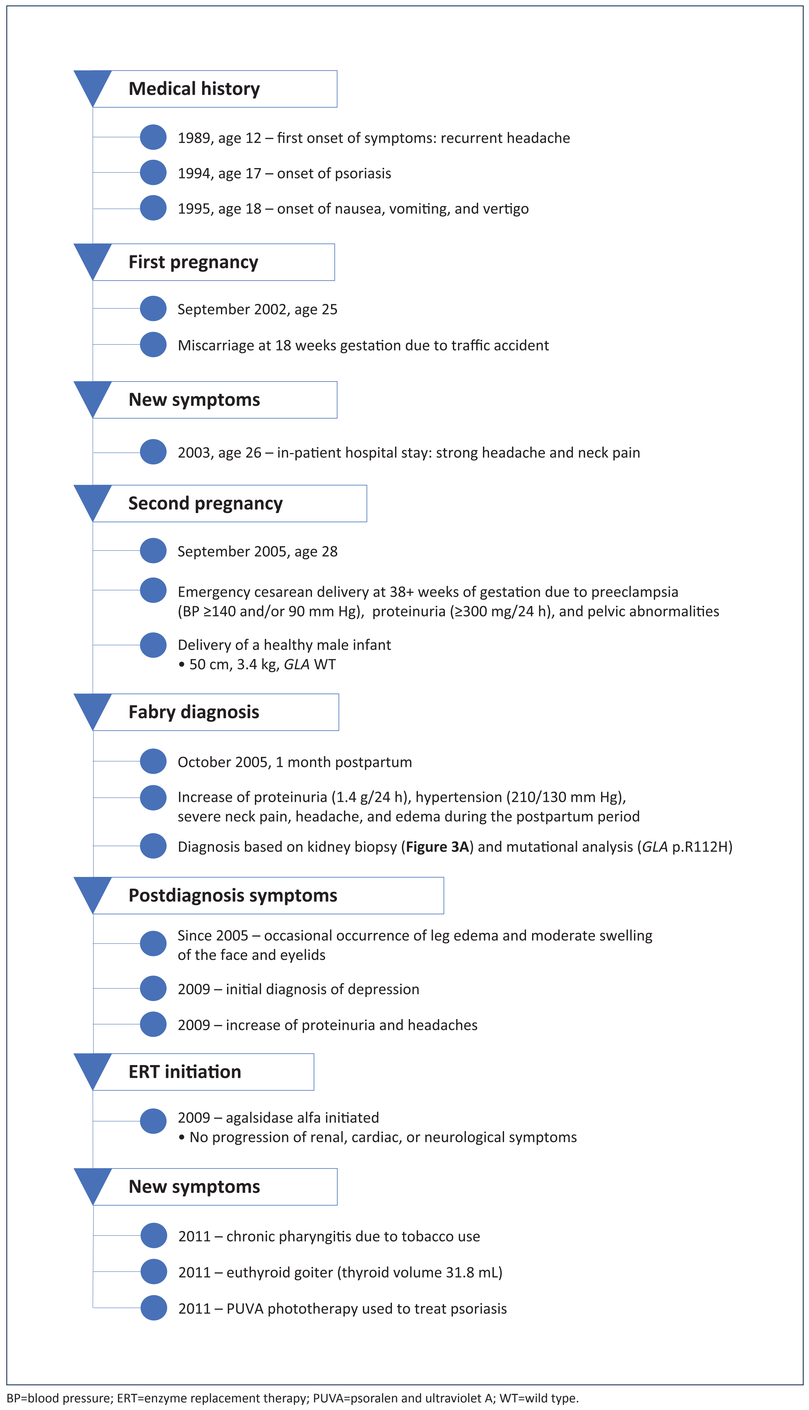
Figure 1. Family Tree



The patient is indicated by the arrow.
Black boxes represent males with Fabry disease; circles with black dots represent females with Fabry disease. Slash indicates deceased.

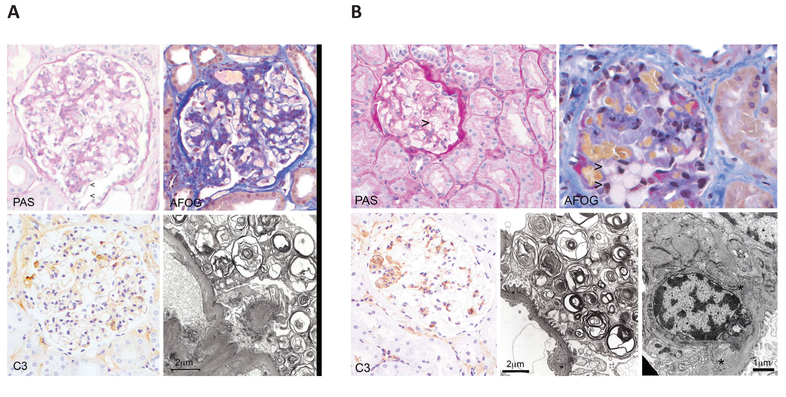
- The patient's medical history prior to migalastat treatment is shown in **Figure 2**

Figure 2. Patient History



BP=blood pressure; ERT=enzyme replacement therapy; PUVA=psoralen and ultraviolet A; WT=wild type.

Figure 3. Images From Kidney Biopsy Showing Fabry Disease and C3 Deposits

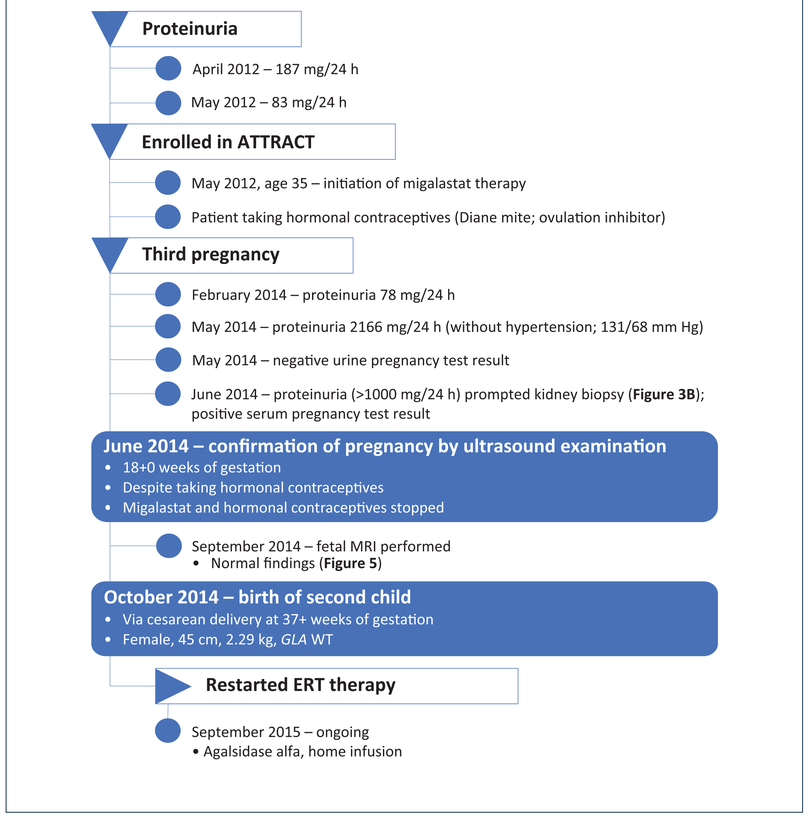


AFOG=acid fuchsin orange G; IgA=immunoglobulin A; IgG=immunoglobulin G; PAS=periodic acid-Schiff; TEM=transmission electron microscopy.
(**A**) The first renal biopsy (2005) shows in >50% of the glomeruli a diffuse, segmentally accentuated mesangial matrix and cell increase (PAS and AFOG), and segmentally obliterated capillary loops adherent to the Bowman's capsule (AFOG). There is dominant segmental C3 deposition (C3) in the absence of IgG and IgA. Podocytes show characteristic lamellar and zebroid bodies by TEM; however, the classical appearance of "foamy" podocytes was less dominant by light microscopy (PAS) due to the segmental nature of the pathological changes.
(**B**) The second renal biopsy (2014) shows characteristic foamy macrophages (PAS and AFOG, >) as well as segmental mesangial matrix and cell increase. Dominant C3 deposits (C3) correspond to mesangial electron dense deposits (*) by TEM (right) while almost all podocytes contain lamellar and zebroid inclusion bodies (left).

Treatment With Migalastat

- Details of migalastat treatment and of the third pregnancy are shown in **Figure 4**

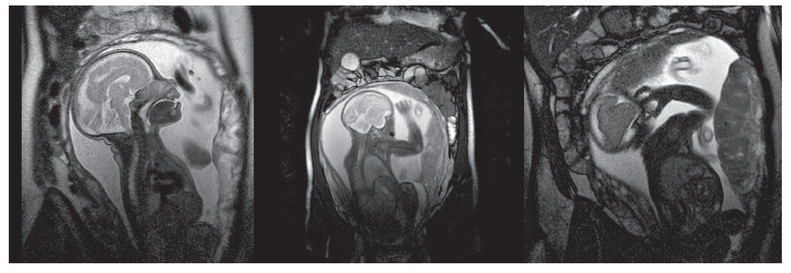
Figure 4. Migalastat Treatment and Pregnancy



MRI=magnetic resonance imaging.

- During the pregnancy, fetal magnetic resonance imaging indicated normal development (**Figure 5**)
- Although the pregnancy was uneventful, the birth weight was low

Figure 5. Fetal MRI (Coronal Plane) During Pregnancy



CONCLUSIONS

- Except for low birth weight, pregnancy outcome in this case was normal despite exposure to migalastat for 18 weeks during the pregnancy
- Migalastat therapy during pregnancy is not advised

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DISCLOSURE

Conflicts of Interest

NH-V has received a travel grant from Amicus Therapeutics and Shire. SE-H, UP, MF, RK, and AS have nothing to disclose. NS and JAB are employees of and hold stock in Amicus Therapeutics. GS-P has served on advisory boards and received honoraria and research funding from Amicus Therapeutics, Shire, and Sanofi.

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