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Safe and Successful Treatment With Agalsidase Beta During Pregnancy in Fabry Disease

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Fabry disease, an X-linked lysosomal storage disorder, is caused by α-galactosidase A deficiency and leads to accumulation of glycospinhgolipids in most tissues, with life-theratening consequences in the kidney, heart, and cerebrovascular system. Enzyme replacement therapy is available as 2 different preparations: agalsidase alfa and agalsidase beta. Enzyme replacement therapy is started as soon as the diagnosis is confirmed, but there is no data available in the literature about its safety during preganacy. Herein, we described 2 patients with Fabry disease who received agalsidase beta during their pregnancy. This report is important as the data about enzyme replacement therapy during pregnancy is restricted with case reports.

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Case Report

INTRODUCTION

Fabry disease is an X-linked inherited storage disorder caused by α-galactosidase A deficiency with an incidence rate of 1 in 40000 to 117000 in the general population.[1] The average age at presentation is 6 to 9 years.[2] Although male patients might be severely affected, majority of heterozygous female patients show the characteristic signs of the disease which has been related to skewed X inactivation by some authors.[3]

Fabry disease is a multisystem disease caused by progressive accumulation of globotriaosylceramide within lysosomes in a variety of cell types that later results in kidney failure, hypertrophic cardiomyopathy, and cerebrovascular disease.[2] Enzyme replacement therapy is used in both sexes, which brings into question the safety of enzyme replacement therapy during pregnancy. We describe 2 patients with Fabry disease who received agalsidase beta during their pregnancy.

CASE REPORT

Case 1

A 26-year-old woman was diagnosed with Fabry disease during a family screening. Her α-galactosidase level was found to be below the reference range (50 pmol per spot × 20 h). Multisystem evaluation showed left corneal opacity and cornea verticillata, upper limb position sense deficit, a serum creatinine level of 0.68 mg/dL, a glomerular filtration rate of 105 mL/min/1.73 m^2, mild proteinuria (400 mg/d), and a stenosis (10.5 × 1.1 mm) of the posterior wall of the left common carotid artery on carotid Doppler ultrasonography (Figure 1). Echocardiographic parameters were in normal range.

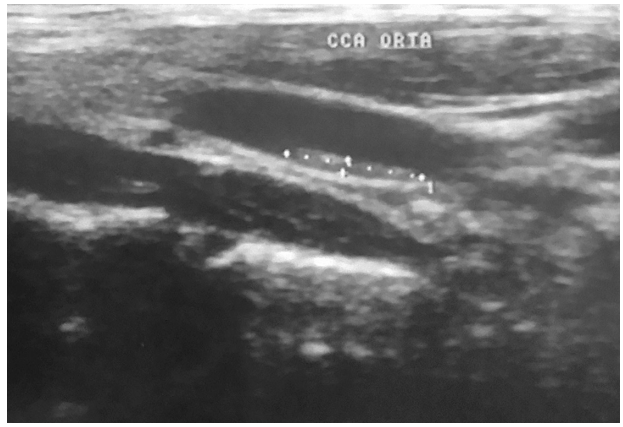

Figure 1. Doppler ultrasonograpghy of the common carotid artery revealed stenosis (10.5 × 1.1 mm) of the posterior wall of the left common carotid artery.

Genetic testing revealed heterozygote L275F mutation in the *GLA* gene. Enzyme replacement therapy with agalsidase beta was considered but she was 8-week pregnant. The patient agreed to start the treatment (1 mg/kg every 2 weeks) accepting any possible risks. During her pregnancy, the tests showed regression of proteinuria (100 mg/d), no pathologic finding on electromyography, a serum creatinine level of 0.63mg/dL and a glomerular filtration rate of 114 mL/min/1.73 m^2. At week 40, she gave birth to a healthy girl; body length of 45 cm and weight of 3100 g. The child had no malformation.

Case 2

A 29-year-old woman was diagnosed with Fabry disease during a family screening. Genetic testing revealed heterozygote L275F mutation in the *GLA* gene. On general examination, she had prominent papules on the scalp and whole body, appearing like angiokeratomas (Figure 2). The patient had suffered from photophobia and acroparesthesia, had mild proteinuria (250 mg/d), and complained of fatigue. Echocardiographic parameters were in normal range. Her creatinine level was 0.72 mg/dL and glomerular filtration rate was 96 mL/min/1.73 m^2.

Enzyme replacement therapy with agalsidase beta (1 mg/kg every 2 weeks) was initiated. At the 2nd month of her treatment, she declared her pregnancy and continued treatment, accepting any possible risks. At week 40, she gave birth to a healthy girl; body length of 51 cm and weight of 3400 g. Postpartum proteinuria, serum creatinine level and glomerular filtration rate were 58 mg/d, 0.69 mg/dL, and 101 mL/min/1.73 m2, respectively.

DISCUSSION

Although Fabry disease is known for decades, enzyme replacement therapy is available since 2001. Most authors suggest initiation of enzyme replacement therapy as soon as the diagnosis is confirmed.[2] Recombinant human α-galactosidase A is available in two forms of agalsidase alfa, given as an intravenous infusion at a dose of 0.2 mg/kg biweekly, and agalsidase beta, given as an intravenous infusion at a dose of 1 mg/kg biweekly.[2] Studies comparing the two forms showed no significance.[4]

Enzyme replacement therapy may prevent irreversible changes in cardiac and renal systems by preventing globotriaosylceramide accumulation if started at an earlier age, but its effect decreases as the disease progresses.[5] Clearance of accumulated globotriaosylceramide reduces the neuropathic pain and gastrointestinal symptoms, stabilizes kidney function, and improves cardiac functions.[6]

Evidence on enzyme replacement therapy during pregnancy is limited only to case reports. In 2005, Wendt and colleagues described the first successful pregnancy outcome in a patient receiving agalsidase alfa.[7] Two more pregnant cases receiving agalsidase alfa were described by Kalkum and colleagues in 2009.[8] No reports describing a patient receiving agalsidase beta was available since Politei[9] and Germain and colleagues[10]

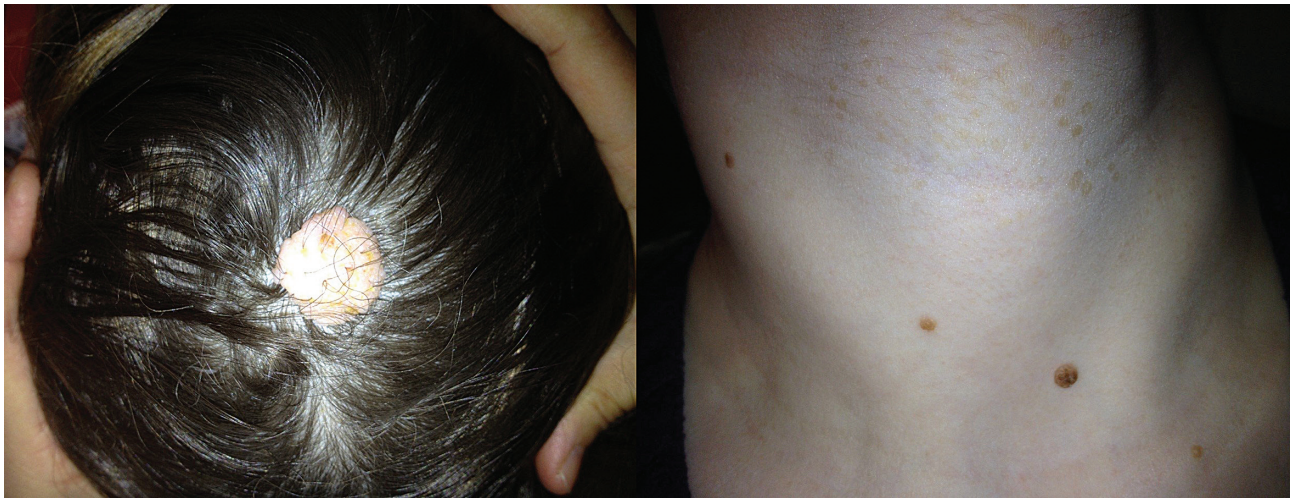

Figure 2. Angiokeratomas on the scalp and the body.

who described 2 uneventful pregnancy outcomes with agalsidase beta. There are still not enough studies to clarify whether the enzyme passes the placental barrier.[11]

Our patients agreed to continue treatment during pregnancy. None of them reported any complications and both gave birth to healthy children. Since the benefits of the enzyme replacement therapy is well known and recurrence of the symptoms might be seen when the therapy is stopped, as well as considering the positive pregnancy outcomes reported, we think that enzyme replacement therapy should be continued during pregnancy. Our cases bring the total number of successful pregnancies during enzyme replacement therapy to 7. As it is a replacement therapy of congenitally deficient enzyme, enzyme replacement therapy during pregnancy may be foreseen harmless. Further studies should be done in pregnant patients to fully understand the benefits and risks of therapy.

CONFLICT OF INTEREST

None declared.

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