A Fabry Disease Patient Who Developed Hypersensitivity Reaction against Agalsidase Beta following COVID-19 Infection

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Abstract
Fabry disease (FD) is a rare, X-linked inherited lysosomal storage disorder, characterized by the accumulation of globotriaosylceramide (Gb3) due to the deficiency or absence of alpha-galactosidase A. Due to the accumulation of Gb3, cardiac, renal, neurological, and skin manifestations can be observed. Enzyme replacement therapy (ERT) with agalsidase alfa or agalsidase beta is the cornerstone in the management of FD. Both enzymes are clinically effective and widely used. In this study, we present a 19-year-old male patient with FD who had received ERT for almost two and half years without any complications. In January 2021, he was diagnosed with COVID-19 infection. Later, he developed an infusion reaction during his first ERT infusion following the resolution of COVID-19 infection. The patient experienced shortness of breath, shivering, and rash. Despite decreased infusion rate and premedication in repetitive infusion, his symptoms were not resolved. Subsequently, he developed an IgE antibody against agalsidase beta, and his skin prick test was positive. Since IgG positivity against agalsidase beta was also detected, agalsidase beta was replaced with agalsidase alfa. The patient did not experience any allergic reaction with agalsidase alfa. Moderate to severe allergic reactions during ERT infusion should be alarming for IgE development. Furthermore, COVID-19 should be considered a trigger for allergic reaction against ERT in patients with FD.

Introduction
Fabry disease (FD) is an X-linked lysosomal glycosphingolipid storage disease and is caused by the absence or deficiency of alpha-galactosidase A (AGAL) enzyme due to the mutation in the galactosidase alpha gene [1]. AGAL deficiency results in progressive accumulation of globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3) in tissues [1]. Glycosphingolipid deposits induce cellular dysfunction, endothelial damage, inflammation, and apoptosis [2]. Cardiac, renal, neurological, and skin manifestations including acroparesthesia, hypohidrosis, angioedema, proteinuria, kidney failure, abdominal pain, cardiomyopathy, arrhythmia, hearing loss, corneal changes (cornea verticillata), transient ischemic attacks, and strokes can be seen in FD [3].
Disease-specific treatment is primarily focused on replacing the missing or deficient enzyme with the recombinant human AGAL alfa or beta enzyme. Enzyme replacement therapy (ERT) includes the administration of agalsidase alfa (0.2 mg/kg every 2 weeks) produced from human cell lines and agalsidase beta (1 mg/kg every 2 weeks) produced from Chinese hamster ovary cell lines, which are the two available pharmaceutical preparations on the market. Both of them have been shown to be clinically effective. In some amenable mutations, migalastat, a pharmacological chaperone that corrects folding errors and restores lysosomal trafficking of the enzyme, might also be used [4, 5].

In this case report, we describe a patient with FD who developed hypersensitivity reaction to agalsidase beta following COVID-19 infection. Informed consent was obtained from the patient for publication of this case report and accompanying images.

Case Presentation

A 19-year-old male patient with an unremarkable medical history was admitted for family screening following his elder brother’s diagnosis with FD. His AGAL level was 0.2 nmol/mL/h (reference level >2.5 nmol/mL/h), and lyso-Gb3 level was 45.9 ng/mL (reference level <1.30 ng/mL). Genetic examination revealed that the patient had the p. R227X mutation of the galactosidase alpha gene. On physical examination, angiokeratomas on his buttocks, elbows, and back were noticed. Hearing and vision screening did not reveal any pathology. Neurological examination was normal. On laboratory examination, his creatinine level was 0.83 mg/dL, e-GFR was 129 mL/min/1.73 m2, and proteinuria was 107 mg/day. On cardiac MRI, septal T1 was decreased, which was compatible with FD. Thus, the patient was diagnosed with FD, and agalsidase beta 1 mg/kg every other week was initiated in August 2017. He has received ERT with full compliance and without any complications. In January 2021, he had a COVID-19 infection, confirmed by the SARS-CoV-2 PCR test. Although he was unvaccinated, he had only mild symptoms including dry cough and runny nose and did not require hospitalization. During his first infusion after he had COVID-19 infection, he experienced shortness of breath, shivering, and an urticarial rash. Two weeks later, even though premedication (pheniramine 45.5 mg and prednisolone 40 mg) was administered, and the infusion rate was lowered from 30 mg/h to 15 mg/h, he had similar symptoms during the enzyme infusion. A workup was performed to reveal the cause of the newly onset allergic reactions. Agalsidase beta IgE antibody was found positive (its titer was 0.52 kUA/L [references: 0.35–0.54 kUA/L low positive, 0.55–1.39 kUA/L moderate positive, 1.40–3.89 kUA/L high positive, and >3.90 kUA/L very high positive]). Complement C3a and tryptase were negative. Due to an allergic reaction, the patient did not receive ERT for almost a year. After this period, he was admitted to our center, and we made an additional workup before the reinstatement of ERT. Total IgE titer was 125.4 IU/mL (reference value <100 IU/mL), and the skin prick test was positive (Fig. 1).

Eosinophilia was not present. Agalsidase beta IgG was also found positive (800 IU/mL [reference value: 100–204.8 IU/mL]). Due to the presence of a high IgE titer, positive prick test, and antienzyme antibodies against agalsidase beta, we considered switching to agalsidase alfa treatment. We also performed a skin test against agalsidase alfa, and following a negative reaction, we reintroduced the ERT with agalsidase alfa with a dose of 0.2 mg/kg every other week. The infusion was administered over a period of 2 h without any premedication. We did not observe any adverse reaction to agalsidase alfa.

Discussion

The temporal association between COVID-19 infection and the development of allergic reactions against ERT might be causal in nature. SARS-CoV-2 might cause symptoms of autoimmune/autoinflammatory disease by immune system hyperactivation in susceptible adults. Even though this symptom is generally experienced temporarily, some patients can suffer from it permanently [6, 7]. Furthermore, hypersensitivity reactions were observed during COVID-19 infection [8]. Therefore, the allergic reaction in our patient could have been triggered by the COVID-19 infection. It could also be suggested that the present case rather demonstrates a nonimmunologic anaphylaxis (also previously known as anaphylactoid response), which indeed might be triggered by an activated immune system due to COVID-19.

IgE development against agalsidase beta has been reported in the literature. Tanaka et al. [9] noted that one of their patients with FD, who had severe atopic dermatitis history, experienced purulent eczema with hyperthermia and IgE development against agalsidase beta following his first agalsidase beta infusion. After the fourth reinfusion, his symptoms disappeared, but eosinophilia became prominent. Therefore, the medication was replaced by agalsidase alfa. No cross-reactivity of the IgE antibody against agalsidase alfa was observed and the treatment was continued without a major side effect [9]. On the other hand, in Bodenstein et al.’s study [10], patients withdrawn from several previous clinical studies due to the detection of IgE or skin prick test positivity against agalsidase beta were gathered, and a rechallenge protocol was administered. In this cohort, one patient had IgE positivity, and five had a positive skin prick test. During reinstatement, no anaphylactic shock was observed, and all patients were able to switch to treatment with commercial drugs. However, information about the patients’ medical history was not available. Even though a successful reinstatement protocol was previously re-
Fig. 1. Skin prick test with agalsidase beta. Different dilutions were marked with arrows; boundaries of the corresponding indurations are marked with pen over the skin.
ported [10], we decided to switch to ERT, based on the result of the skin prick test performed with both drugs and the presence of agalsidase beta-specific IgE reactivity.

The emergence of IgG against agalsidase alfa and agalsidase beta is common in repetitive ERT. In earlier studies, although a partially impaired Gb3 clearance has been observed in patients with circulating anti-agalsidase IgG antibodies, a direct correlation between IgG production and clinical outcome has not been found [11, 12]. However, subsequent studies emphasized that patients who had anti-agalsidase antibodies had a lower glomerular filtration rate and a greater left ventricular mass. Additionally, those patients suffered more frequently from neuropathic pain, diarrhea, and fatigue [13, 14]. Therefore, the presence of IgG antibodies might be associated with reduced ERT efficacy.

Conclusion

Patients who develop moderate to severe allergic reactions during ERT should be carefully monitored and screened for IgE development. A recent COVID-19 infection might facilitate those allergic reactions in these patients, where ERT might be considered.

Statement of Ethics

The present work was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Ozge Sonmez, Seyda Gul Ozcan, and Nurhan Seyahi: conception or design, or analysis and interpretation of data, or both; drafting the article or revising it; providing intellectual content of critical importance to the work described; and final approval of the version to be published. Sinan Trabulus: drafting the article or revising it and final approval of the version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article.

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