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Anti-Taliglucerase Alpha Antibodies Associated with Lower Efficacy of ERT and Onset of Autoimmune Thyroiditis in a Patient with Type 1 Gaucher Disease

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Abstract

Treatment of patients with Gaucher disease type 1 with enzyme replacement therapy might be associated with development of anti-drug antibodies. As we know, the literature is lacking reports demonstrating the development of ADAs in patients with GD1 and association with a decreased efficacy, as was shown in other LSDs. We elaborate that high levels of ADAs in a patient with GD1 have impeded the hematologic endpoints and biomarker levels improvements and may have triggered autoimmune thyroiditis.

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Introduction

Gaucher Disease (GD) is one of the most frequent lysosome storage disease that affects glycolipids metabolism. It results from the deficiency of lysosomal acid beta glucocerebrosidase enzyme, due to mutations in GBA1. Gaucher disease is the first glycolipid storage disorder to be treated safely and effectively with intravenous glucocerebrosidase Enzyme Replacement Therapy (ERT) [1]. The decision to offer ERT in patients with non-neuronopathic Gaucher disease type 1 is based upon disease severity, as determined by the initial assessment, or significant disease progression, as demonstrated through regular follow-up [2]. Taliglucerase alfa is an ERT approved for the treatment of adult and pediatric patients with Type 1 GD (GD1). It is

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the first plant cell-expressed recombinant therapeutic protein approved by the US Food and Drug Administration for humans. Studies report good efficacy and safety of taliglucerase alfa in treating patients with GD1, either children or adults [3-5]. Nevertheless, treatment with taliglucerase alfa can be associated with the production of anti-drug antibodies, generally not affecting the efficacy of the drug [5,6]. The purpose of this report was to show a case where the presence of high levels of ADAs in a patient with GD1 treated with taliglucerase alpha is associated with decreased efficacy and development of an autoimmune Hashimoto thyroiditis in this patient, which we believe had served as a trigger.

A 37-year-old female diagnosed with GD1 at the age of 29 years. The first signs of the disease appeared around 19 years old, with hemorrhagic skin manifestations, epistaxis and hepatosplenomegaly. Complete blood count showed thrombocytopenia and anemia, while bone marrow aspiration was interpreted as normal.

At the age of 23 years, the patient had a twin pregnancy that ended in spontaneous abortion followed by an extrauterine pregnancy some months later. At 26 years old, she had a normal pregnancy, a successful C-section delivery that was complicated with high fever, thrombocytopenia and anemia. In consultation with gastro-hepatologist (due to suspicion for autoimmune hepatitis), the patient was treated with corticosteroids with minimal improvement.

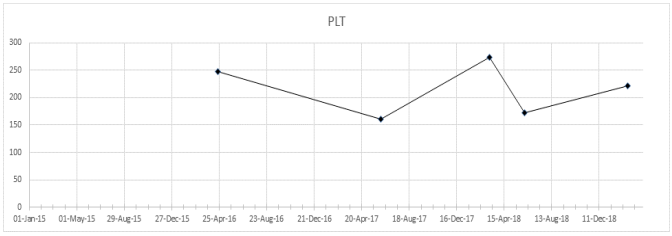
Diagnosis: At 29 years old, due to persisting hematologic disturbances and the new onset of bone pain, another bone marrow aspiration was performed, which demonstrated the presence of Gaucher cells. The activity of the glucocerebrosidase enzyme was very low, which confirmed the diagnosis of Gaucher disease. Genetic testing identified the presence of c.1226A>G mutation (N370S, old nomenclature), as well as the double mutation of c.1342G>C (D409H, old nomenclature); c.882T>G (H255Q, old nomenclature), thus the genotype N370S/ D409H; H255Q (old nomenclature) was determined.

Treatment initiation with Enzyme Replacement Therapy (ERT): In March 2012, at the age of 31 years, it was made possible to start treatment with Imiglucerase (Cerezyme), which continued until December 2014. At this time, treatment was switched to taliglucerasealfa (due to non-medical reasons) and continued with the same dose; 50 Kg/weight every other week.

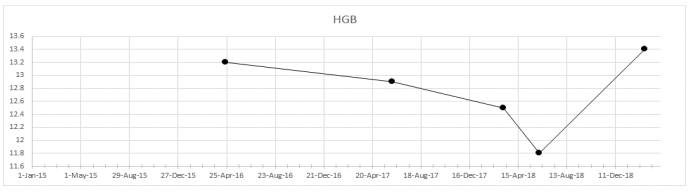
Clinical evolution: Treatment with ERT was associated with the gradual improvement of the hematologic parameters as well as with the improvement of the biomarkers (chitotriosidase and lyso-Gb1 performed at The Institute of Child Health, Athens, Greece and Centogene laboratory, Rostock, Germany, respectively) (Figure 1). After more than two years of ERT with taliglucerase alfa, in May 2017, the patient reported a shortening of the menstrual cycle. At this time, the laboratory tests showed an increase of TSH to10.2 μUI/ml (N= 0.4-4.0 μUI/ml) with the presence of anti-thyroid peroxidase antibodies (anti-TPO), 1690 UI/ml (N<34 UI/ml). An ultrasound of the thyroid gland demonstrated heterogenicity of the gland with micro and macro nodules, the largest of 8-10 mm. Thyroid' scintigraphy revealed the presence of zones with different fixation of the radioactive contrast, with uptake at the minimum of normal levels. Based on these data, the diagnosis of autoimmune thyroiditis was established and levothyroxine was added to the treatment regimen. Further family history revealed several family members with autoimmune and/or inflammatory diseases, including rheumatoid arthritis, diabetes mellitus, thyroiditis, asthma and pancreatitis (Figure 2).

Laboratory testing performed at that time showed decreased platelet counts and decreased hemoglobin levels parallel to increased biomarkers levels (Figure 1). There were not noticed any change in liver and spleen volume as well as in parameters. In August 2018, ERT was switched to velaglucerase alpha. Laboratory tests show improved hematological parameters and decreased biomarkers level (Figure 1).

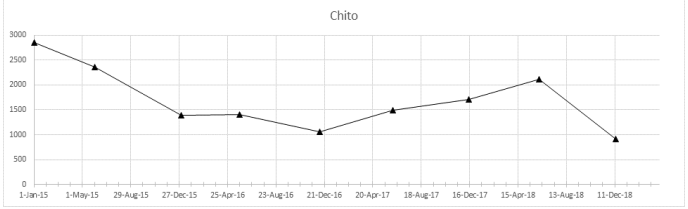
During treatment with taliglucerase alfa, blood samples have been drawn and preserved in 70 degrees every six months in order to be tested for the presence of anti taliglucerase antibodies, as part of our clinical protocol. Testing was enabled in January 2019 (Covance Laboratory, Indianapolis, USA), showing negative results during the first year of therapy with a progressive increase anti-taliglucerase alfa titers (Figure 1).



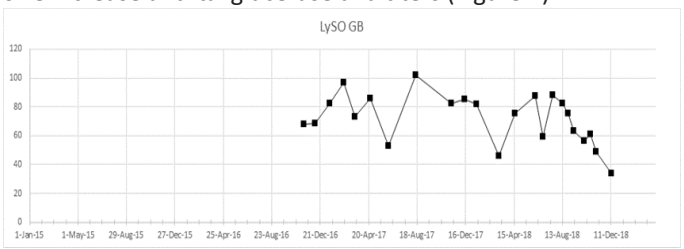
(a) Platelet count



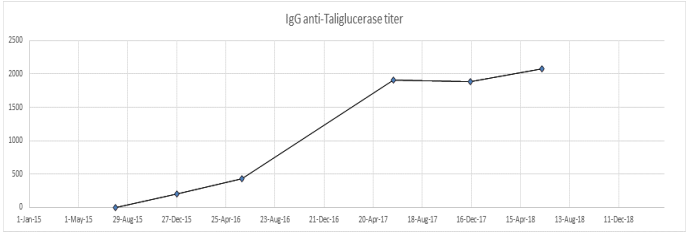
(b) Hemoglobin level



(c) Chitotrioxidaselevel



(d) Lyso-Gb1 levels



(e) Anti-Taliglucerase antibodies levels.

Figure 1: Changes over time of **(a)** platelet count, **(b)** hemoglobin level, **(c)** chitotriosidase, **(d)** lyso-Gb1 levels.

(e) Anti-Taliglucerase antibodies titer

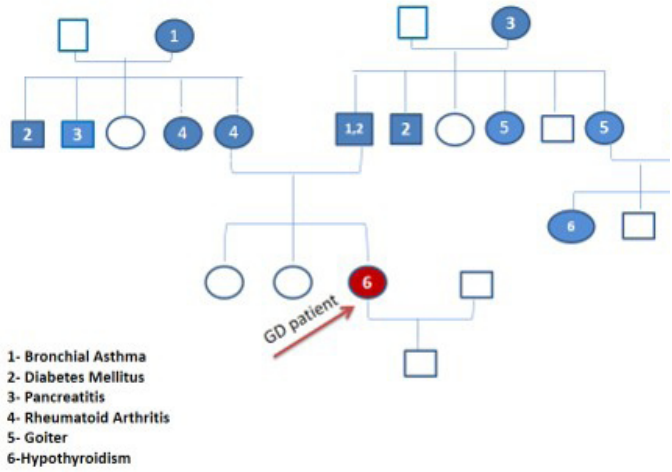


Figure 2: Pedigree of patient's family.

Discussion

The introduction of ERT in the treatment of LSD has significantly changed the evolution of these diseases. However, the evidence has demonstrated that the therapeutic enzymes induce an immune response that may manifest with hypersensitivity reactions and/or antibodies production (ADAs) [6-9]. The presence of ADAs was associated with a decrease in drug efficacy, as shown, especially in Pompe disease and a lower rate in Mucopolysaccharidosis (MPS); MPS1, MPS2, MPS6 [10-13]. The effect of ADAs on the clinical efficacy may be related to a reduction in enzyme stability, increased enzyme degradation, antibody-mediated blockade of cell receptor uptake, retargeting of Mannose 6P-glycosylated (M6P) enzyme to macrophages and intracellular misrouting of ERT [14,15].

Since patients with GD1 have residual enzyme activity, the immune system can tolerate the exogenous ERT resulting in less risk for developing ADAs [7]. Still, the production of ADAs was reported in patients with GD1 treated with all three currently used types of ERT; imiglucerase, velaglucerasealfa and taliglucerase alfa [6,15-18]. The presence of ADAs against ERT was not predictive for drug-related hypersensitivity reactions, although the risk might be higher [6,8]. Our experience in 27 GD1 patients treated with taliglucerase alfa supports these findings; eight developed hypersensitivity reactions such as urticaria, pruritus, lip edemaetc., but only one was found to have a very low titer of ADAs. The one patient with a relatively severe hypersensitivity reaction did not have any ADAs (unpublished data). The presence of ADAs in patients with GD1 was shown not to affect the efficacy of the enzyme [6,16]. The lack of neutralizing antibodies was suggested to be related to the uptake of the ADAs by the macrophages, the target cell in GD [7].

In the present case, we show that high levels of ADAs can decrease the drug efficacy also in a patient with GD. As autoimmune thyroiditis developed at the same time, we suspected that the ADAs served as a trigger for the development of associated autoimmune disease. One can speculate that the family predisposition to autoimmune diseases and the late start of treatment with ERT made her immune system more vulnerable to the therapeutic enzymes [17].

We switched to velaglucerase alfa considering the fact that probable cross-reacted antibodies do not affect the efficacy of ERT as reported by Elstein and Zimran [18,19]. In our patient, the initiation of velaglucerase alfa was associated with improvement in all parameters including platelet count, hemoglobin level, GB1 level and activity (Figure 1).

The development of autoimmune thyroiditis at the same time as the increase in the ADA levels is another illustration ofthe immune system imbalance in GD. Similarly, others have reported an association between GD and autoimmune disorders such as lupus [20], hemolytic anemia [21], immune thrombocytopenia [22] and bullous pemphigoid [23].

Conclusion

In conclusion**,** our report shows that also in GD, the presence of high levels of ADAs may lead to a decrease in the efficacy of ERT and may serve as a trigger for developing an autoimmune disease. In those cases, we recommend switching thetype of ERT and monitoring closely.

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