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CASE REPORT

Enzyme Replacement Therapy in a Patient with Gaucher Disease Type III: A Paradigmatic Case Showing Severe Adverse Reactions Started a Long Time After the Beginning of Treatment

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Abstract *Introduction:* There are three recombinant enzymes available for the treatment of Gaucher disease (GD): imiglucerase, velaglucerase alfa, and taliglucerase alfa.

Case report: A male GD type III patient, 14 years old, genotype p.L444P/L444, diagnosed at 2 years old. He had been treated with imiglucerase for 9 years since the diagnosis. In 2008, however, he presented a severe adverse reaction to imiglucerase, characterized by cough, laryngeal stridor, and periorbital edema. The infusions were suspended for 3 months when imiglucerase was restarted with premedication and a slower infusion rate. After 5 months, he presented a new adverse reaction with vomiting, tachypnea, cough, and periorbital edema. Intradermal testing confirmed IgE-mediated reaction but serological tests were negative. After 2 years and 10 months with no specific treatment and a significant worsening of the clinical picture, taliglucerase alfa was prescribed, with premedication and a slower infusion rate. At the first infusion, he presented moderate adverse reaction and the infusions were suspended. After 2 months, velaglucerase alfa was initiated uneventfully. He maintains day-hospital infusions without premedication and shows improvement of clinical and laboratory parameters.

Conclusion: This is the first report of the use of velaglucerase alfa in patients with GD type III. The use of recombinant enzymes is safe for the majority of GD patients, but severe reactions may occur even many years after the beginning of the treatment. Premedication and slower infusion rate reduce the incidence of adverse reactions but may not solve the problem. This case report further demonstrates the different safety profile among all the recombinant enzymes available for the treatment of GD.

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Introduction

Gaucher disease (GD) is the most common lysosomal storage disorder, with an estimated worldwide incidence of

1 per 57,000 live births in the general population (Meikle et al. 1999) and up to 1 per 850 live births among Ashkenazi Jews (Mistry et al. 2011). Classically, GD is subdivided into three main forms (types I, II, and III), defined by clinical characteristics, disease course, and ethnic prevalence. Nevertheless, there is a wide range of findings that overlap across the classical forms, which has led to a new assessment of GD as a continuous spectrum of disorders rather than a disease with three distinct subtypes (Beutler and Grabowski 2001; Sidransky 2004).

The incidence of subacute neuronopathic (type III) GD is approximately 1 per 100,000 live births. Its distribution is ubiquitous, although the populations of some regions in Northeast Sweden are disproportionately affected (Dahl et al. 1990). Patients with GD type III may exhibit systemic manifestations similar to those of type I patients. Neurological involvement may arise at any age, and usually presents as epilepsy, ataxia, vertical gaze palsy, or dementia (Davies et al. 2007). Some patients may have corneal opacities and valvular heart disease with progressive calcification. The life expectancy is 20–30 years (Tylki-Szymanska and Czartoryska 1999).

For many years, GD was managed with supportive care and palliative measures alone, such as splenectomy to mitigate growth delays, cytopenias, and abdominal discomfort due to splenic enlargement. Since the 1990s, enzyme replacement therapy (ERT) has been the treatment of choice. ERT has improved quality of life among GD patients by reversing many signs and symptoms (Mistry et al. 2007; Hollak et al. 2009). However, the amount of enzyme required to maintain quality of life and reverse the course of symptoms is controversial. Until 2009, imiglucerase (Genzyme Corporation, Allston, MA), obtained from Chinese hamster ovary (CHO) cell lines, was the only ERT agent available. New alternatives have since entered the market, such as velaglucerase alfa (Shire HGT, Dublin, Ireland), which is obtained from human cells and received FDA and EMA approval in 2010, and taliglucerase alfa (Protalix, Carmiel, Israel), which is obtained from carrot cells and received FDA approval in 2012. Despite the longer history of imiglucerase, studies have shown that all three recombinant enzymes are similar in terms of efficacy (Elstein 2011). Approximately 1% of patients develop adverse reactions to imiglucerase ERT, which can be related or not to the production of IgG or IgE antibodies against the synthetic enzyme, forcing judicious use of maintenance infusions. The rate of infusion reactions appears to be higher with taliglucerase alfa and lower with velaglucerase alfa (Zimran et al. 2011; Morris 2012). Substrate reduction therapy with miglustat (Zavesca®, Actelion Pharmaceuticals, Freiburg, Germany) is also available and is mostly indicated for adult GD patients in whom ERT is contraindicated (Platt et al. 1997; Cox et al. 2000; Pastores et al. 2005). The results of therapy with eliglustat (Genzyme Corporation, Allston, MA), another substrate reduction agent, appear promising, but it is still at the clinical trial stage (Lukina et al. 2010).

The management of GD type III is hindered by the fact that recombinant enzymes cannot cross the blood–brain barrier efficiently and act on the CNS. In patients with neuronopathic GD, enzyme dosage is currently adjusted according to the severity of visceral manifestations, with the maximum dosage being 60 IU/kg/infusion every 2 weeks (Vellodi et al. 2009).

This report describes the case of a patient with GD type III who has received all three recombinant ERT forms available, the adverse effects to each formulation, and the clinical outcomes obtained.

Case Report

A 14-year-old male received a diagnosis of GD type III (β-glucocerebrosidase activity, 2 nmol/h/mg [reference range: 10–45]; genotype p.L444P/L444P) at age 2 due to hepatosplenomegaly, kyphoscoliosis, horizontal supranuclear gaze palsy, and cognitive and pulmonary involvement. During workup, the patient was found to be heterozygous for a 24-bp duplication in exon 10 of the *CHIT1* gene, causing partial chitotriosidase deficiency. Shortly after diagnosis, the patient was started on imiglucerase ERT (60 IU/kg/infusion every 2 weeks) at our hospital. Two years after the start of treatment, a central venous catheter was implanted so the patient could receive infusions at his hometown, located 360 km from our service; infusions were provided this way for a total of 4 years and after this through a peripheral access, although the central venous catheter was not removed. Nine years after the start of treatment, while receiving an infusion at a local health facility in his hometown, the patient developed a severe adverse reaction characterized by cough, laryngeal stridor, and periorbital edema within 5 min of the start of infusion. The infusion was ceased at once and the patient was given IV dexamethasone and oral dexchlorpheniramine, with complete resolution of symptoms. C3 and C4 levels were within normal limits, and the IgE level was 1629 UI/mL (reference range for age, <200 UI/mL) 4 days after the adverse event. We chose to discontinue ERT and wait for the results of the serum anti-imiglucerase antibody test, which was performed by the drug manufacturer and carried out on a blood sample collected 40 days after the reaction. The patient remained ERT-free for 3 months waiting for the results of testing, which were ultimately negative for anti-imiglucerase IgG and IgE antibodies (ELISA). Therefore, imiglucerase ERT was restarted at the same dosage (60 IU/kg/infusion every 15 days), now at our service, in a hospital

setting, with loratadine 10 mg PO as premedication and a slower rate of infusion (total infusion time 2 h 30 min). As the patient did not develop any adverse reactions to this scheme, infusions were restarted at his hometown after the third post-reaction infusion. Four months later, the patient developed another reaction, now presenting as vomiting, redness at the catheter site (we could not ascertain whether this was associated with a catheter-related infection), tachypnea, cough, and periorbital edema of 40 min duration. The infusion was ceased and the patient received hydrocortisone 400 mg IV, with complete resolution of symptoms. After this episode, ERT was again discontinued and the patient underwent skin testing for hypersensitivity. The test was performed in two stages, in an ICU setting, in accordance with a test protocol provided by the drug manufacturer. The first step, consisting of a similar standard prick test for common allergens, was negative. The second test included intradermal testing, whereby doses of increasingly concentrated imiglucerase were injected into the dermis. An IgE-mediated reaction was confirmed by the appearance of a >20-mm wheal-and-erythema response within 15 min of injection of imiglucerase 1:10 and 1:100. In view of the anaphylactoid nature of the reaction and the good clinical condition of the patient, we chose to discontinue imiglucerase treatment altogether. Furthermore, neither miglustat nor velaglucerase/taliglucerase alfa were available in the public health system in Brazil at the time (2008).

The patient continued to receive regular follow-up every 3 months for monitoring of clinical and laboratory parameters. At 34-month follow-up, as the patient's condition had deteriorated significantly (episodes of epistaxis, hepatosplenomegaly, hypoalbuminemia, and lower extremity edema) and taliglucerase alfa had recently become available in Brazil, and after discussing this option with the patient's family and securing their informed consent, as patients with allergic reactions to imiglucerase were excluded from clinical trials of taliglucerase alfa, we decided to attempt ERT with this novel medication. The patient was premedicated with loratadine 10 mg PO, ranitidine 150 mg PO, and hydrocortisone 400 mg IV and the infusion rate was titrated slowly (1 mL/15 min, 2 mL/15 min, 4 mL/15 min, 8 mL/15 min, 16 mL/15 min, and 32 mL thereafter). However, after infusion of 5.8 mL of taliglucerase alfa at a dosage of 60 IU/kg, the patient developed epigastric pain, vomiting, rash, and headache. Dexchlorpheniramine 2 mg PO, promethazine 25 mg IV, and metoclopramide 10 mg IV were administered and there was improvement of symptoms. The infusion was halted and the decision was made to discontinue taliglucerase alfa therapy. Two months after this reaction, velaglucerase alfa was provided for this patient as a compassionate use. After discussing this option with the patient's family and securing their informed consent, as no data were available on treatment of GD type III with this enzyme, the decision was made to attempt ERT once more. An anti-imiglucerase antibody test performed by Shire HGT in November 2011 (electrochemiluminescence immunoassay for anti-imiglucerase and anti-velaglucerase antibodies) was negative for IgG and IgE antibodies.

The patient was admitted to our hospital for stabilization of clinical parameters and a battery of tests to determine baseline laboratory values. After 2 weeks of hospitalization, velaglucerase alfa was administered at a dosage of 60 IU/kg, after premedication with hydrocortisone 400 mg IV and promethazine 25 mg IV and an infusion rate titrated to 200 mL over the course of 4 h. The infusion was completed uneventfully, and the patient was started on twice-monthly infusions on an outpatient basis. Premedication was gradually reduced over the course of five sessions, with no ill effects. After eight infusions at our hospital, the patient returned to his hometown, where he continues to receive periodic infusions. He no longer requires premedication and the infusion time has been shortened to 2 h. We chose to wait for further clinical improvement before removal of the central venous catheter.

The patient's neurological condition remains stable and his anemia, hyperproteinemia, and lower extremity edema have resolved completely. Thrombocytopenia has improved substantially and abdominal volume and chitotriosidase levels are reduced (Table 1). In addition to these improvements in objective parameters, application of the SF-36 and WHOQoL questionnaires (completed by proxy by the patient's mother) revealed improvement in quality of life (data not shown).

Discussion

Recombinant enzyme replacement therapy is safe for most GD patients, but 1.5% to 25% may develop adverse reactions, depending on the medication regimen (Starzyk et al. 2007; Zimran et al. 2011). Some reports have described premedication and manipulation of infusion rates for the management of imiglucerase-related adverse effects (Peroni et al. 2009), but these measures are not always effective. In view of a worldwide shortage of imiglucerase (Hollak et al. 2010), the Brazilian National Health Surveillance Agency (ANVISA), the regulatory counterpart of the U.S. FDA and the European EMA, granted emergency marketing authorization for taliglucerase alfa in 2010. In 2011, an updated version of the Brazilian Ministry of Health guidelines for GD disease was approved, which included all the three recombinant enzymes available on the market (imiglucerase, taliglucerase alfa, and velaglucerase alfa) and substrate reduction therapy (miglustat). Currently, there are Brazilian patients on all four forms of treatment. Although X-ray structures of all three enzymes are very similar, they show some differences in their sequence and glycan structure. Taliglucerase alfa has

Table 1 Follow-up of laboratory parameters and imaging findings

	Pre-treatment[b]	Before first imiglucerase reaction	34 months without treatment	Before first velaglucerase alfa infusion	After 6 velaglucerase alfa infusions	After 12 velaglucerase alfa infusions
Age (years)	2	11	13.3	14.3	14.6	14.9
Height (cm)[a]	73	122	132	132	132	132
Weight (kg)	9.0	23.6	29.7	29.7	30.1	31
Hemoglobin (g/dL)	8.3	13	8.6	8	10.7	12.6
Platelets (1,000/mm^3)	133	280	65	56	62	115
Chitotriosidase (nmol/mL/h)	8,627	1,808	15,117	19,878	15,814	13,074
Liver[c]	8.2 cm (longest axis)	889 cm^3	Normal	5,367 cm^3	5,369 cm^3	ND
Spleen[c] (longest axis, in cm)	12.1	9.5	17.5	27	17	ND
Albumin (g/dL)	ND	ND	3	2.9	ND	3.48
Bone changes[d]	Kyphoscoliosis	Kyphoscoliosis	Osteolytic and osteoblastic lesions, Erlenmeyer flask deformity, and kyphoscoliosis	ND	ND	ND
BMD (T score)	−5.7	ND	−4.6	ND	ND	ND
BMB score	ND	ND	ND	14	ND	ND
Spirometry	ND	FEV1/FVC: 73% – air flow preserved	FEV1/FVC: 34.5 % – severe restrictive ventilatory defect	FEV1/FVC: 31.3 % – severe restrictive ventilatory defect	ND	ND
Severity Score Index (SSI)[28]	24	28	31	33	32	29

[a] Difficult to measure due to bone changes

[b] Shortly before first imiglucerase infusion

[c] On ultrasound

[d] On X-rays

BMD Bone mineral density – DEXA (Z score was not available), *BMB score* bone marrow burden (MRI), *FEV_1* Forced expiratory volume in 1 s, *FVC* Forced vital capacity, *ND* Not done

two additional amino acids at the N-terminus, and it has additional seven amino acids at the C-terminus in relation to the "wild" human counterpart. Besides that, the amino acid composition of both imiglucerase and taliglucerase alfa differs from the human β-glucocerebrosidase at residue 495. Velaglucerase alfa has the same amino acid sequence as the human enzyme. Regarding the glycosylation process, taliglucerase alfa differs from the other two enzymes as it contains xylose and fucose derivatives, which are unique to plant-derived proteins (Brumshtein et al. 2010).

Despite no detectable serum anti-imiglucerase IgE or IgG antibodies, our patient had a positive intradermal test response and almost instant adverse response to imiglucerase (after 9 years of infusions without any intercurrence) and taliglucerase alfa (at the first infusion). This may be indicative of a hypersensitivity reaction to some element present during the manufacturing process of imiglucerase – an element possibly used in manufacturing of taliglucerase alfa as well. The patient does not seem to present an hyper-IgE syndrome since he did not present any clinical symptoms associated with hyper-IgE syndrome such as skin abscesses, recurrent pneumonia, pneumatoceles, early eczema, and late loss of primary dentition (Sowerwine et al. 2012).

Interestingly, our patient presented an anaphylactoid reaction after many years of imiglucerase ERT. This could have implications for some countries in which home therapy is widely available; for safety reasons, we suggest the patient should not be alone during home infusions.

Throughout the course of this case, we attempted to follow existing adverse reaction management protocols for patients with GD and other lysosomal storage disorders (Kim et al. 2008) and create our own, but the patient could not adapt to imiglucerase or taliglucerase alfa ERT despite these measures. Miglustat was not trialed because, despite marketing approval, there was no available stock at the time of the patient's reactions. Furthermore, the patient was extremely debilitated and underweight, and was thus not a candidate for substrate reduction therapy.

After the availability of other recombinant forms of β-glucocerebrosidase in several countries in 2010, the scenario for management of patients who tolerate imiglucerase poorly or have discontinued ERT for other reasons has improved, as the switch to substrate reduction therapy (Elstein et al. 2007) or another recombinant enzyme has proved safe and effective (Elstein et al. 2012; van Dussen et al. 2012).

This is the first report of velaglucerase alfa therapy in a patient with GD type III. We suggest, on the basis of our findings, although this enzyme has not received formal approval for use in patients with GD type III, it should be assessed for use in such patients who develop adverse reactions to imiglucerase or taliglucerase alfa. The Brazilian Ministry of Health guidelines for treatment of GD does not mention any contraindications to the use of velaglucerase alfa in patients with type III disease. In addition to describing the success of velaglucerase alfa therapy, this report demonstrates the differences in safety profile of the three enzymes available for ERT for Gaucher disease for this patient, which are most likely related to distinct manufacturing processes and can occur at any time after the beginning of therapy.

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Contributors

FV designed data collection, monitored data collection, analyzed the data, drafted and revised the paper. He is the guarantor. AD, CN, SM, MW, DD, KM, CBR, AQ, TV, TN, and SL analyzed the data, and revised the paper. IVDS designed data collection, monitored data collection, analyzed the data, drafted and revised the paper.

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