Management of Neutralizing Antibody to Ceredase in a Patient With Type 3 Gaucher Disease

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ABSTRACT. Objectives. The beneficial effects of macrophage-targeted glucocerebrosidase (Ceredase) in patients with Gaucher disease are well established. A minority of recipients develop transient nonneutralizing antibodies to the exogenous enzyme. A 7-year-old patient with type 3 Gaucher disease whose clinical course began to deteriorate while receiving Ceredase developed a progressively increasing titer of IgG antibody that blocked the catalytic activity of Ceredase. We sought to develop a strategy that would restore the benefit of enzyme replacement therapy in this patient.

Methods. The patient was treated with two courses of a combination of plasma exchange, cyclophosphamide, intravenous IgG, and large doses of Ceredase.

Results. After the second course of this regimen, the titer of the neutralizing antibody in the blood gradually declined to negligible levels. Clinical parameters that had been deteriorating (reduction of hemoglobin level, increased serum acid phosphates activity, repeated skeletal infections, progressive enlargement and infarction of the spleen) all improved. There has been no recurrence of the neutralizing antibody in this patient.

Conclusions. Very few patients with Gaucher disease who are treated with Ceredase develop a neutralizing antibody to the exogenous enzyme. In the rare instances where this phenomenon occurs, it is likely that the strategy we have used (plasma exchange, cyclophosphamide, intravenous IgG, and large doses of enzyme) may provide benefit to such individuals. It is also likely that this technique may be helpful when enzyme replacement therapy is attempted in patients with other disorders in which the genetic mutation abrogates the production of the protein (CRIM-negative individuals). Pediatrics 1997; 100(6). URL: http://www.pediatrics.org/cgi/content/full/100/6/e11; Gaucher disease, neutralizing antibody, Ceredase.

ABBREVIATIONS. NIH, National Institutes of Health; MRI, magnetic resonance imaging; IgG, immunoglobulin G; IVIG, intravenous IgG.

Gaucher disease is an autosomal recessive lipid storage disorder caused by a deficiency of the enzyme glucocerebrosidase.1 Patients have been classified into three clinical phenotypes. The most prevalent of these is type 1, nonneuronopathic Gaucher disease. Signs and symptoms in this category include anemia, thrombocytopenia, hepatosplenomegaly, and skeletal damage, but no apparent brain involvement. Patients with types 2 (acute neuronopathic) and 3 (chronic neuronopathic) Gaucher disease show early and late onset, respectively, of central nervous system damage.2 The benefit of enzyme replacement therapy with macrophage-targeted glucocerebrosidase (Ceredase, Genzyme Corp, Cambridge, MA) in patients with type 1 Gaucher disease has been demonstrated conclusively.3–10 Similar trials have been undertaken in patients with type 3 Gaucher disease in whom remarkable reduction of hepatosplenomegaly and improvement of skeletal damage have been documented.11 At present, a major uncertainty regarding enzyme replacement therapy in type 3 patients is whether this intervention will reverse, prevent, or delay the occurrence of neurologic signs, such as horizontal gaze paresis and myoclonic epilepsy, that are characteristic of type 3 Gaucher disease.12 Resolution of these aspects requires extensive investigation in patients with this phenotype.

One of the patients in the enzyme therapy trial in type 3 Gaucher disease11 was a boy of age 5 years, 4 months. He had undergone a partial splenectomy at 5 years and 1 month. The procedure was followed by recurrence of massive splenomegaly. Treatment with Ceredase was initiated at a dose of 60 U per kilogram of body weight every other week. After striking initial beneficial responses, the patient gradually developed a neutralizing antibody to Ceredase that resulted in recurrence of hematologic and skeletal complications characteristic of untreated patients with aggressive Gaucher disease.12 We report here the design and application of a strategy that resulted in a dramatic reduction of his antibody titer and the reappearance of the characteristic benefits from enzyme replacement therapy.

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METHODS

Patient

The patient was born on March 4, 1986. He was first seen at the National Institutes of Health (NIH) on February 29, 1988. He was suspected of having type 3 Gaucher disease because of massive hepatosplenomegaly, anemia, thrombocytopenia, and poorly initiated horizontal saccadic eye movements. The diagnosis was confirmed by assaying glucocerebrosidase activity in his white blood cells, which revealed a level of 5.7% of normal activity. Over the next 2½ years, he was evaluated periodically at NIH. Because of progression of his hepatosplenomegaly and worsening of anemia and thrombocytopenia, he underwent a partial splenectomy without incident at Children’s National Medical Center, Washington, DC, on May 22, 1991. We have not been able to identify this patient’s genotype. It is known to be distinctly different from the genetic mutations that have been identified in other patients with type 3 Gaucher disease seen at the NIH.12

Because of persistent hepatomegaly and reenlargement of his spleen, the child was readmitted to NIH on July 24, 1991. He was entered into an Intramural Review Board-approved study of enzyme replacement therapy, and treatment was begun at 60 U of Ceredase per kilogram of body weight every 2 weeks. Enzyme infusions were administered on the ward or in the day hospital at NIH. A physical examination was performed, and hematologic parameters were determined at each visit.

Clinical Course

The patient was admitted to NIH for periodic evaluation on January 21, 1992, 6 months after the initiation of enzyme replacement therapy. Substantial reduction of hepatosplenomegaly had occurred since the preceding admission. His hematologic status was within normal limits for his age. The horizontal gaze palsy had not changed. Neuropsychologic testing revealed that memory and fine and gross motor skills were below normal for his age. He had not changed. Neuropsychologic testing revealed that memory and fine and gross motor skills were below normal for his age. He had not changed. Neuropsychologic testing revealed that memory and fine and gross motor skills were below normal for his age. He had not changed. Neuropsychologic testing revealed that memory and fine and gross motor skills were below normal for his age. He had not changed. Neuropsychologic testing revealed that memory and fine and gross motor skills were below normal for his age. He had not changed.

RESULTS

Detection of Neutralizing Antibody

The patient began to develop increasing titers of an antibody that blocked the catalytic activity of Ceredase in May 1992, 10 months after starting enzyme replacement therapy (Fig 1). The antibody was found to be an immunoglobulin G (IgG). Moreover, the IgG anti-Ceredase subtypes that developed in this patient were different from those seen in other patients with Gaucher disease who developed IgG antibodies.15 In this individual, there was a significant IgG1, IgG2, and IgG4 response. Previous patients with Gaucher disease who developed nonneutralizing antibodies to Ceredase developed IgG1, and many had IgG3 antibodies. Relatively few had IgG2 or IgG4 subtypes. The production of inhibitory IgG antibodies has been reported in patients with hemophilia A treated with factor VIII.16 The untoward consequences of the neutralizing antibody to Ceredase in our patient with type 3 Gaucher disease became overt in the early part of 1993 when he had a reduction in his hematocrit and platelet levels concomitant with an increase in serum acid phosphatase. On July 6, 1993, he had a second bony infarct, this time in his right proximal humerus. Abdominal MRI revealed worsening hepatosplenomegaly as well as a new infarct in his splenic remnant. A third bony infarct occurred in his left distal femur in October 1993.

The presence of the neutralizing antibody significantly altered the pharmacokinetics of infused glucocerebrosidase in the blood (Fig 2). Except in this patient, intravenous administration of 60 U of Cere-
dase per kilogram of body weight to patients with Gaucher disease causes a characteristic rise of glucocerebrosidase activity in the blood that reaches a steady state. Glucocerebrosidase activity in blood declines rapidly after cessation of the enzyme infusion. In this child, there was only a slight rise in glucocerebrosidase activity in the blood, and the time course differed dramatically from that in all the other patients with type 1 and type 3 Gaucher disease that we have treated (Fig 2).

**Intervention**

Because of rapid progression of hematologic and skeletal complications and a mounting titer of neutralizing antibody, we felt that measures to decrease the antibody level were clinically indicated. Immune tolerance has been induced in patients with hemophilia who developed antibodies to factor VIII by combination therapy consisting of intravenous IgG (IVIG), cyclophosphamide, and large doses of factor VIII. We wished to determine whether a similar strategy combined with plasma exchange would reduce the neutralizing antibody in this patient with Gaucher disease. Accordingly, an initial treatment schedule was carried out as outlined in Table 1. In addition to cyclophosphamide, infusions of high levels of Ceredase, and IVIG, we performed three 1-vol plasma exchanges on alternate days.

**Reduction of Neutralizing Antibody Titer**

The effort to immunosuppress the patient was initiated on July 26, 1993. He underwent plasmapheresis, using 5% albumin in saline as the replacement fluid, three times on alternate days. He received one intravenous infusion of 15 mg of cyclophosphamide per kilogram of body weight on the first day of treatment, and he was given a daily oral dose of 2 mg/kg of cyclophosphamide from days 2 to 10. He was administered 0.4 mg of IVIG per kilogram of body weight daily over a period of 5 days, starting on the fifth day, for a total dose of 2 g/kg. In addition, he was given 60 U/kg of Ceredase intravenously every other day for a total of five infusions.

Following this regimen, there was a temporary reduction of antiglucocerebrosidase antibody in his serum (Fig 1). The antibody titer subsequently rose over the next 2 months to a mean of 1:29. Abdominal MRI revealed increasing hepatomegaly and evidence of an infarct in the remaining portion of the spleen. In mid-October 1993, he had an infarct of his left distal femur. The antiglucocerebrosidase antibody titer was 1:16 at that time. His hemoglobin level had decreased to 92 g/L, but his platelet count was in the normal range (263 × 10^9/L). Acid phosphatase was 2.8 U/L (normal, 0.0 to 0.4). Alkaline phosphatase level was 328 U/L (normal for a child this age, >500 U/L). Because of his worsening condition, a second, more intensive course of immunosuppressive therapy was initiated on November 28, 1993 (Table 2).

For the second course, the patient underwent a single plasmapheresis on day 1. Cyclophosphamide (15 mg/kg) was administered intravenously on days 1 and 2. He then received 2 mg/kg of cyclophosphamide orally for the next 30 days. A 5-g loading dose of IVIG was administered on the first day of this treatment cycle after the plasma exchange. Additional doses (400 mg/kg body weight) were administered on days 4 through 8. Augmented doses of Ceredase were given according to the following schedule: days 1 to 3, 120 U/kg of body weight; days 4 through 10, 60 U/kg body weight. High doses of Ceredase (120 U/kg of body weight) were continued weekly. Three weeks into this course of immunosuppressive therapy, titers remained unchanged at a mean of 1:19 that continued over the next 4 months. From months 33 to 42, the neutralizing antiglucocerebrosidase antibody titer declined gradually to near normal levels (Fig 1). At 60 months, the pharmacokinetic profile of glucocerebrosidase in the blood was found to be normal (Fig 2).

**Clinical Response**

By March 1994 (44 months), the patient’s hemoglobin level had risen to 107 g/L. In July 1994, his hemoglobin level was 105 g/L, and the acid phosphatase level had decreased to 1.4 U/L. A decrease in the size of his liver was found on MRI in August 1994. His infusions of Ceredase were decreased to 60 U per kilogram of body weight per week. In January 1995, his hemoglobin level was 106 g/L, acid phosphatase level 1.6 U/L, and platelet count 237 × 10^9/L.

**TABLE 1. Initial Immunosuppressive Schedule**

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PE indicates plasma exchange (one plasma volume); CTX, cyclophosphamide; GC, macrophage-targeted glucocerebrosidase (Ceredase).
10^9/L. By September 1995, his liver and spleen had decreased still further, and in October 1995, his hemoglobin level was 119 g/L. The skeletal abnormalities had stabilized, and the neutralizing antibody was only intermittently detectable at a titer of ≤1:2.

CONCLUSIONS

The occurrence of antibodies to Ceredase in patients with Gaucher disease receiving enzyme replacement therapy is uncommon. In the majority of patients in whom nonneutralizing anti-Ceredase antibodies occurred, they receded spontaneously without an adverse effect on patients’ response to enzyme replacement therapy. The present case, however, revealed that harmful consequences can arise when an antibody is produced that interferes with the catalytic activity of Ceredase. The development of a strategy that suppressed production of the neutralizing antibody was particularly salutary in this case. At this time, we do not know which specific intervention (cyclophosphamide, IVIG, large doses of Ceredase, or plasma exchange) was the primary factor in ameliorating this patient’s condition. The gradual reduction in the titer of neutralizing antibody over many months of continued exposure to high doses of Ceredase suggests that this may have been an important factor. In a trial in which immune tolerance was induced in patients with hemophilia A who developed antibodies to factor VIII, the investigators concluded that it was necessary to use a combination of cyclophosphamide, IVIG, large doses of factor VIII. Until evidence of the effectiveness of one of the agents we used alone, or of a specific combination of agents, becomes available, we feel that the seriousness of the consequences of a neutralizing antibody to Ceredase in patients with clinically aggressive Gaucher disease warrants the use of the combination of cyclophosphamide, IVIG, large doses of Ceredase, and plasma exchange. This conclusion is supported by the report of unsuccessful reversal of neutralizing antibody in a patient with type 1 Gaucher disease who was treated with Cytoxan and weekly infusions of 60 U/kg of Ceredase. Although the cost of the second course of Ceredase in our patient has been estimated to be in the range of $100 000, it should be borne in mind that this phenotype of Gaucher disease is fatal if not treated successfully.

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