Nine healthy deliveries in four pregnant women with enzyme replacement therapy in Gaucher disease

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Abstract

Aim: Our aim is to present the pregnancy and delivery cases that occurred with successful enzyme replacement therapy (ERT) in our female Gaucher patients, whom we have followed and treated for years.

Materials and Methods: We tried to retrospectively evaluate and present 9 pregnancy and delivery events that occurred with successful ERT in 4 of our 32 Gaucher patients, whom we have been following up and treated for years in our clinic. Patient monitoring parameters include regular clinical, biological, and radiological evaluations. We checked our Gaucher’s disease (GD) patients regularly at regular intervals before and during pregnancy for their hemoglobin, platelet, leukocyte, ferritin, blood sugar and creatinine levels.

Results: 4 of the 32 cases were children, age range (4-16 years), 16 women age range (22-68 years), 12 men age range (34-72 years). Four of our cases have not received treatment yet. 12 of the female cases are receiving regular ERT (3 months-14 years). Of the male cases, 9 were receiving ERT (3-9) and 3 were not taking medication. One of our cases gave birth to a total of 4 children, first twins and then two single children with an interval of 3 years. Two of our patients had two deliveries and one of our patients with both Gaucher and SLE disease gave birth. Pregnant patients came to check-ups more frequently during pregnancy and were followed up and treated with a multidisciplinary approach each time they came. The ERT treatments of the patients were increased during pregnancy as the patient gained weight, and the symptoms that increased during pregnancy were relieved by increasing the dose.

Conclusion: As a result, in our study, we observed that there was a healthy and successful pregnancy and delivery with ERT, which was started at the appropriate time and given at the appropriate dose. Comprehensive studies involving more cases are required in this regard.

Introduction

Gaucher’s disease (GD) is a rare autosomal recessive genetic disease characterized by accumulation of glucocerebroside in cells of the macrophage-monocyte system. GD disease is a rare metabolic disorder that develops due to an error in the recycling of cellular glycolipids. This disease is caused by a deficiency of the enzyme glucocerebrosidase. GD is the most common lysosomal storage disease that occurs as a result of mutation of the β-glucocerebrosidase enzyme (GCase), which causes the accumulation of non-degradable glucocerebroside (monosaccharide) and other glycolipids in tissues such as spleen, bone marrow and liver. In GD, severe enlargement of the spleen and liver, cytopenias, bone pains and bone crises are seen. Clinical findings occur due to deposits in the bone, bone marrow, kidneys, and lungs [1]. The incidence of GD rises to 1/800 in Ashkenazi Jews, while it is approximately 1/40,000 to 1/200,000 births in the general population. The carrier frequency is 6% in Jews, compared to 0.7% to 0.8% of the non-Jewish population.

There are 3 main types of GD depending on the central nervous system involvement: non-neuropathic (type I), acute neuropathic (type II) and chronic neuronopathy (type III). There are 2 rarer subtypes, the perinatal-lethal form and the cardiovascular form. Type I affects the spleen, liver, bone and bone marrow, Type II GD presents with severe neurological symptoms in early childhood and death usually occurs before 2 years of age. Type III may also have significant visceral and pulmonary involvement, apart from neurological symptoms that are less severe than type II 11 [3,4]. 95% of Gaucher’s cases are GD type 1 and
it is the most common form in adults. GD type 1 GD1 presents with splenomegaly, blood disorders, orthopedic complications and absence of neurological symptoms, while GD type 2 presents with hepatosplenomegaly and central nervous system involvement in the first year of life. In addition, GD type 3, which manifests itself with nervous system involvement in childhood. These forms of the disease share the same defect in the enzyme glucocerebrosidase; however, different subtypes help establish the correct diagnosis and subsequent treatment plan [4-6].

To diagnose a patient with GD, hepatosplenomegaly, thrombocytopenia +/- anemia, characteristic bone lesions, or additional central nervous system (CNS) involvement in GD2 or GD3 are required [7]. However, clinical findings alone are not diagnostic; The presence of GD biomarkers is also required. The current gold standard for the diagnosis of GD is the demonstration of decreased β-glucocerebrosidase (GCase) activity in peripheral blood cells, together with mutation analysis at the DNA level of the glucocerebrosidase gene (GBA1) performed by whole gene sequence [1,2]. The diagnosis is confirmed by measuring glucocerebrosidase activity in peripheral blood leukocytes. Less than 15% of the mean normal activity is diagnostic [1,2].

The main symptoms of type 1 GD (increased bleeding risk, anemia, splenomegaly, hepatomegaly, and bone disease) are likely to affect women during reproductive events such as menarche and menstruation; fertility, pregnancy, parity, childbirth and lactation; and menopause. In the past, it was believed that GD patients could not get pregnant easily and could not have a healthy baby because of these problems [1,2]. After the introduction of enzyme replacement therapies (ERT) into clinical use, it was seen that many of the problems previously seen in GD patients could be overcome. It was observed that growth and development retardation decreased with ERT, menarche and bleeding problems, and the rates of miscarriage and still-birth in pregnant women were significantly reduced in the treated patients. A study by Zimran et al. evaluated the effects of ERT on menstruation, pregnancy and menopause in women. In this study, they reported that ERT had positive effects on both menarche, pregnancy and menopause in these cases [8].

In this study we conducted, we aimed to present the results of 9 healthy pregnancies and births in 4 of our 32 GD patients that we have followed for years. This study is the first study in our country on Gaucher patients and fertility, excluding case reports.

Materials and Methods

Ethical approval was obtained from Malatya Turgut Ozal University Non-Interventional Clinical Research Ethics Committee before the study (Date: 26.05.2022, Decision number: 2022/102). We tried to retrospectively evaluate and present 9 pregnancy and delivery events that occurred with successful enzyme replacement therapy in 4 of our 32 Gaucher patients, whom we have been following up and treated for years in our clinic. The clinical, laboratory and radiological parameters of the patients were evaluated and recorded. The gynecology and obstetrics clinic considered these patients as risky patients and followed them regularly and the results were recorded. Gaucher cases routinely come to receive drug treatment every 14 days, and those who do not receive drug treatment come for control every 3 or 6 months at the latest. At each control, Dual energy X-ray Absorptiometry (DEXA) images are taken to evaluate the clinical, laboratory, biochemical and radiological, echocardiographic and bone structures of the patients at appropriate intervals and the results are recorded.

Results

Of the 32 cases, 4 were in the age range of children (4-16 years old), 16 were females (22-68 years old), and 12 were male (34-72 years old). Four of our cases have not received treatment yet. 12 of the female cases are receiving regular ERT (3 months-14 years). Of the male cases, 9 were receiving ERT (3-9) and 3 were not taking medication. One of our cases, who became pregnant during the treatment, gave birth to twins 12 years ago, 3 years and 6 later, a total of 4 children. One of our two patients gave birth twice. One patient with chronic liver disease and esophageal varical bleeding had two deliveries, and one patient with both Gaucher and SLE disease gave birth (Table 1). Pregnant patients came to check-ups more frequently during pregnancy and were followed up and treated with a multidisciplinary approach each time they came. The obstetrics clinic followed these pregnant women in more detail as risky pregnancies. When the pregnant women started to gain weight and their pregnancy progressed, the enzyme replacement therapy was initially 30U/kg, and the dose was increased according to weight, first 45U/kg, and if necessary, 60U/kg according to weight and symptoms. When the dose of ERT used in our pregnant women who had increased bone and joint pain after the second trimester of pregnancy was increased, it was observed that the symptoms and complaints decreased. Bone pain started in the second trimester of pregnancy in our twin patient, and as the gestational week increased, the patient’s symptoms increased, and the amount of ERT administered was increased almost every two weeks, thereby relieving pain and other symptoms. During delivery, 450 cc of blood was lost and 1 unit of erythrocyte suspension was given. At the same time, the symptoms were relieved when the dose of ERT, which was taken in addition to the Rheumatology consultation and recommendations, was increased due to the increase in bone pain during pregnancy in a patient with SLE and GD. In this patient, it was observed that the bone crises that had been present since the beginning of the treatment increased during pregnancy and it was observed that the bone crisis attacks decreased and disappeared with the increased ERT dose. During delivery, two of our pregnant women had bleeding between 240 cc and 450 cc. Only one patient required erythrocyte suspension. In one of our patients whose platelet value decreased below 80.000/ml during pregnancy, platelet level increased when the dose of ERT was increased. It was observed that thrombocyte values of our patients were normalized in a short time after delivery. GD was detected in the two children of our patient who gave birth, aged 4
and 8 years. The treatment has not been started yet, the children are being followed.

Discussion
GD is a rare genetic characterized disease by glucocerebroside accumulation in the cells of the macrophage-monocyte system [1]. GD is a congenital metabolic disorder that affects the recycling of cellular glycolipids. This disease is the result of a deficiency of the enzyme glucocerebrosidase. It causes bone pain, anemia, organ enlargement, abdominal pain and problems with bruising and bleeding. There are many types of GD, all causing similar symptoms in organs and bones [1-3]. Some forms of the disease also affect the brain. There is no cure for GD, but a variety of treatments can help control symptoms, prevent irreversible damage, and improve quality of life. ERT is the primary treatment for GD [1,2]. Treatment of GD is divided into two categories, enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) [9]. The Food and drug administration (FDA) has approved both Cerezyme (imiglucerase) and VPRIV (velaglucerase alfa) for the enzyme replacement therapy of GD types 1 and 3 [10]. ERT does not correct the underlying genetic defect and only alleviates signs, symptoms and ongoing damage caused by toxin accumulation. ERT can improve non-neurological signs and symptoms associated with type 3 GD, as it reduces hepatosplenomegaly and hematological manifestations, often alleviates skeletal manifestations of GD, promotes growth spurt in children, and improves health-related quality of life [11]. In our study, we observed a significant increase in the number of platelets and erythrocytes, and significant reductions in the size of the liver and especially the spleen, compared to the first time we started ERT treatment. Likewise, with the treatment, reduction and disappearance of bone pains and bone crises occurred both before and during pregnancy. A Zimran et al.’s study evaluating the effects of ERT on menstruation, pregnancy and menopause in women of reproductive age, reduced the risk of spontaneous abortion in those who received ERT (1.7% vs. 13.8%), a reduction in the risk of Gaucher-related complications by 1% in untreated 39.4. It was found to be 6.5% in treated patients. Similarly, they stated that postpartum complications related to GD were decreased by 7% in those who received treatment and 21.1% in those who did not [8]. No undesirable effects have been observed in infants breastfed by mothers taking alglucerase and/or imiglucerase to date. The effect of ERT on menopause in Gaucher patients requires further study, particularly with regard to bone pathology [8,12]. In our study, bone pain and bone crises of pregnant women decreased with ERT, menstruation occurred in 3 of the cases with menstrual irregularity at the beginning of the treatment, and pregnancy occurred afterwards, and a healthy baby was born as a result. It was observed that the bleeding seen at birth improved with ERT and the complications related to GD were not observed at the end of the delivery. We continued ERT treatment, which we started before pregnancy, throughout pregnancy and postpartum breastfeeding, and we did not observe any side effects in infants and mothers. In the study conducted by Y Elkstein et al. on 43 women who gave birth to 66, which they followed for 5 years, it was reported that live birth was 86.03% in those who received ERT treatment and 78.3% in those who did not [12]. Since they have more severe clinical findings, bleeding complications were seen more in those who received ERT, but it improved with treatment [12,13]. In our country, E Korkmazer et al. reported a successful pregnancy with ERT treatment and a healthy baby followed for 2 years in a 31-year-old female patient with GD, they continued that ERT prevented spontaneous abortion in this pregnant woman and continued ERT during the postpartum breastfeeding period [14]. The cytopenias seen in GD may resolve in a relatively short time, whereas hepatosplenomegaly decreases more slowly, often over a two-year period. Recovery in bone abnormalities is usually observed after 2 to 4 years of treatment, but some abnormalities persist irreversibly (sequelae of hepatic or splenic fibrosis and bone infarction) [15]. Osteopenia and osteoporosis of bones, bone fractures can be seen in GD patients. Specific ERT therapy remains the best treatment for GD-related osteopenia and osteoporosis. Bisphosphonates should not be used in osteopenia and osteoporosis in premenopausal GD patients. They are often indicated in cases of persistent osteoporosis, especially in postmenopausal women [16]. This is the first and largest study in our country on successful pregnancy and healthy delivery with ERT in GD. As a result, although it is a rare disease, GD, which is not uncommon and we encounter in our clinical practice, can occur at any age. In these cases, with the introduction of ERT into clinical use since the 1990s, improvements in thrombocytopenia, anemia, bone pain and bone crisis occur in the disease, and even successful pregnancies and deliveries can be achieved with ERT in cases that are started at an appropriate time and followed closely. In our study, we observed that with close and regular follow-up and a multidisciplinary approach, GD patients could have healthy pregnancies and deliveries.

Conclusion
GD is a rare disease characterized by organomegaly, thrombocytopenia, anemia, and bone pain and bone crises. It has been observed that the negative effects and complications that may occur in GD have decreased considerably

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Disease</th>
<th>Births</th>
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<tbody>
<tr>
<td>1</td>
<td>Gaucher's disease</td>
<td>Twin births initially and two single births three and six years later</td>
</tr>
<tr>
<td>2</td>
<td>Gaucher's disease</td>
<td>Two births three years apart</td>
</tr>
<tr>
<td>3</td>
<td>Gaucher’s disease and chronic liver disease</td>
<td>Two births three years apart</td>
</tr>
<tr>
<td>4</td>
<td>Gaucher’s disease + SLE</td>
<td>One birth</td>
</tr>
</tbody>
</table>

Table 1. Pregnancy and number of births in Gaucher’s disease patients.
with enzyme replacement therapy for the last 3 decades. As in the normal population, ERT given in the appropriate dose and duration in pregnant cases also shows improvement in GD patients in conditions such as growth retardation, menarche, childbirth and menopause. In our study, we observed that there was a healthy and successful pregnancy and delivery with ERT, which was started at the appropriate time and given at the appropriate dose. Comprehensive studies involving more cases are required in this regard.

Ethics approval

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References