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Pediatric Gaucher experience in South Marmara region of Turkey

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Background/aims: *The aim was to represent the clinical characteristics of six children with Gaucher disease and to describe the results of three years' enzyme replacement therapy.* ***Material and Methods:*** *The data of six Gaucher patients treated with imiglucerase for more than three years were collected. Age, gender, anthropometric measurements, physical examination findings, ophthalmological evaluations, blood counts, liver function tests, liver and spleen sizes, and bone mineral density of the patients were recorded. Clinical presentations, progressions and therapeutic achievements were evaluated.* ***Results:*** *At the time of diagnosis, all patients were clinically type 1 Gaucher disease. Bone lesions, thrombocytopenia and hepatosplenomegaly were found in all patients at diagnosis. After three years of therapy, normalization of blood cell counts, liver and spleen sizes, bone mineral density, and growth was achieved in all patients. Two patients developed neurological symptoms on enzyme replacement therapy, and the diagnosis in these patients was changed to Gaucher type 3. We observed progression of vertebral bone lesions in three patients despite treatment.* ***Conclusions:*** *The results of enzyme replacement therapy are satisfying, but the possibility of deterioration in clinical findings despite therapy should be kept in mind.*

Key words: Gaucher disease, children, treatment results

Türkiye'de Güney Marmara bölgesinin pediatrik Gaucher deneyimi

Amaç: *Gaucher hastalığı tanısı ile izlenmekte olan altı çocuk hastanın klinik bulgularının ve üç yıllık tedavi sonuçlarının sunulması amaçlanmıştır.* ***Yöntem:*** *Üç yıldan daha uzun süre imiglucerase tedavisi almış olan altı hastanın verileri incelendi. Yaş, cinsiyet, antropometrik ölçümler, fizik bakı bulguları, oftalmolojik değerlendirme, tam kan sayımı, karaciğer fonksiyonları, karaciğer-dalak boyutları, ve kemik mineral dansitesi ölçümleri kaydedildi. Başvuru sırasındaki klinik bulgular, hastalık seyri ve tedavi sonuçları değerlendirildi.* ***Bulgular:*** *Tanı sırasında tüm hastalar klinik olarak tip 1 Gaucher hastalığı özelliği göstermekteydi. Kemik lezyonları, trombositopeni ve hepatosplenomegali tüm hastalarda mevcuttu. Üç yıl tedaviden sonra tüm hastaların kan değerleri, karaciğer ve dalak boyutları ve büyüme durumları normal sınırlara ulaştı. İki hastada enzim replasman tedavisi altında iken nörolojik tutulum gözlendi ve tanıları tip 3 Gaucher hastalığı olarak değiştirildi. Ayrıca tedaviye rağmen üç hastada vertebral kemik lezyonlarında ilerleme gözlendi.* ***Sonuç:*** *Enzim replasman tedavisi başarılı sonuçlar vermektedir ancak tedaviye rağmen bazı hastalarda klinik bulgularda kötüleşme olabileceği akılda tutulmalıdır.*

Anahtar kelimeler: Gaucher hastalığı, çocuk, tedavi sonuçları

INTRODUCTION

Gaucher disease (GD), the most common lysosomal disorder, is caused by mutations of the glucocerebrosidase (GBA) gene. Accumulation of the glucocerebroside in monocyte-derived macrophages leads to hepatosplenomegaly, anemia, thrombocytopenia, pulmonary disease, and destructive bone disease. Classically, there are three defined types of GD disease based on the absence or presence of neurological findings. GD type 1, the non-neuronopathic variant, accounts for approximately 94% of patients and is differentiated from the acute neuronopathic/type 2 disease (1%) and chronic neuronopathic/type 3 disease (5%) by the absence of central nervous system involvement. Spe-

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cific enzyme replacement therapy (ERT), imiglucerase, has been shown to be safe and effective in children with Gaucher types 1 and 3 disease (1). Treatment strategies and therapeutic goals of Gaucher patients were declared previously by the International Collaborative Gaucher Group. The treatment is life-long, with high-dose initial therapy and with reduced dose maintenance therapy after the achievement of therapeutic goals (2,3).

This study presents the clinical characteristics of six Turkish children with GD and the results of three years' ERT with imiglucerase.

MATERIALS AND METHODS

The data of six Gaucher patients were collected. The patient group included four patients with type 1 and two patients with type 3 GD, and all of them were on imiglucerase therapy for at least three years. The diagnoses of patients were made based on clinical symptoms and confirmed by genotyping.

Height-weight percentiles, blood cell counts, ultrasonographic long axes of the liver and spleen, and bone mineral density (BMD) were measured periodically. Thorax computed tomography (CT), spinal and femoral magnetic resonance imaging (MRI), and neurological examinations were done annually.

The liver and spleen sizes were followed up with ultrasonographic measurements of longitudinal axes of the liver and spleen during the first two years of therapy. After the second year, liver and spleen volumes were obtained with volumetric CT scans.

The assessments of laboratory findings were done according to the definitions of the International Collaborative Gaucher Groups (2,3), and the interpretation of therapy success was done according to previously defined "therapeutic goals" (4) (Table 1).

Table 1. Therapeutic goals in Gaucher disease

- **Anemia:** increase of hemoglobin concentration to 12 g/dl in 12-24 months of therapy
- **Thrombocytopenia:** normalization of platelet count by 1 year of treatment
- **Hepatomegaly:** reduce liver volume to 1-1.5 times normal
- **Splenomegaly:** reduce spleen volume to 2-8 times normal
- **Skeletal pathology:** lessen or eliminate bone pain within 1-2 years of therapy
- **Growth:** achivement of normal weight and height within 3 years of therapy

RESULTS

The median age of the patients at the diagnosis was 9.5 years (range: 0.75-15 years) and the median duration of ERT was 46 months (range: 37-48 months). The main symptoms were failure to thrive and abdominal distension. None of the patients had neurological involvement at presentation, so the diagnoses of all patients were considered as type 1.

All patients had thrombocytopenia, splenomegaly, hepatomegaly, failure to thrive, bone lesions, and osteoporosis at the time of diagnosis. Anemia was observed in four patients.

After the third year of ERT, the improvements in liver and spleen sizes, blood cells, BMD, and growth status of patients were statistically significant when compared with the initial evaluations. Ultrasonographic long axes of the liver and spleen were normalized in all patients (Figure 1). In concordance, volumetric CT scan revealed achievement of target volume for the spleen in five of six patients, but mild hepatomegaly persisted in all. Only one patient, the patient with type 3b disease, had persistent splenomegaly.

Effects of treatment on blood cells were observed after the first year of ERT (Figure 1).

All patients had achieved catch-up growth at the end of the third year (Figure 2). Medullary involvement of the femur and vertebrae was present in all patients in the beginning. These lesions persisted, and moreover, vertebral collapse, intervertebral bulging, and kyphosis developed in three patients despite ERT.

Bone mineral density (BMD) normalization was achieved in four patients. Osteoporosis in the other two patients did not respond to ERT. Alendronate therapy was started and the results were satisfying, with achievement of normal BMD within the first year of therapy (Figure 1).

During follow-up, two patients' diagnoses were changed from type 1 disease to type 3: One patient with hepatosplenomegaly and pancytopenia had been diagnosed as Gaucher type 1 at the age of 9 months. The neurological examination was normal. Imiglucerase was started with a dose of 60 U/kg/2 weeks at the age of 15 months. After the first year of ERT, he developed strabismus, and ophthalmologic examination revealed horizontal gaze palsy, the characteristic initial symptom of type 3 disease. He was considered as type 3b di-

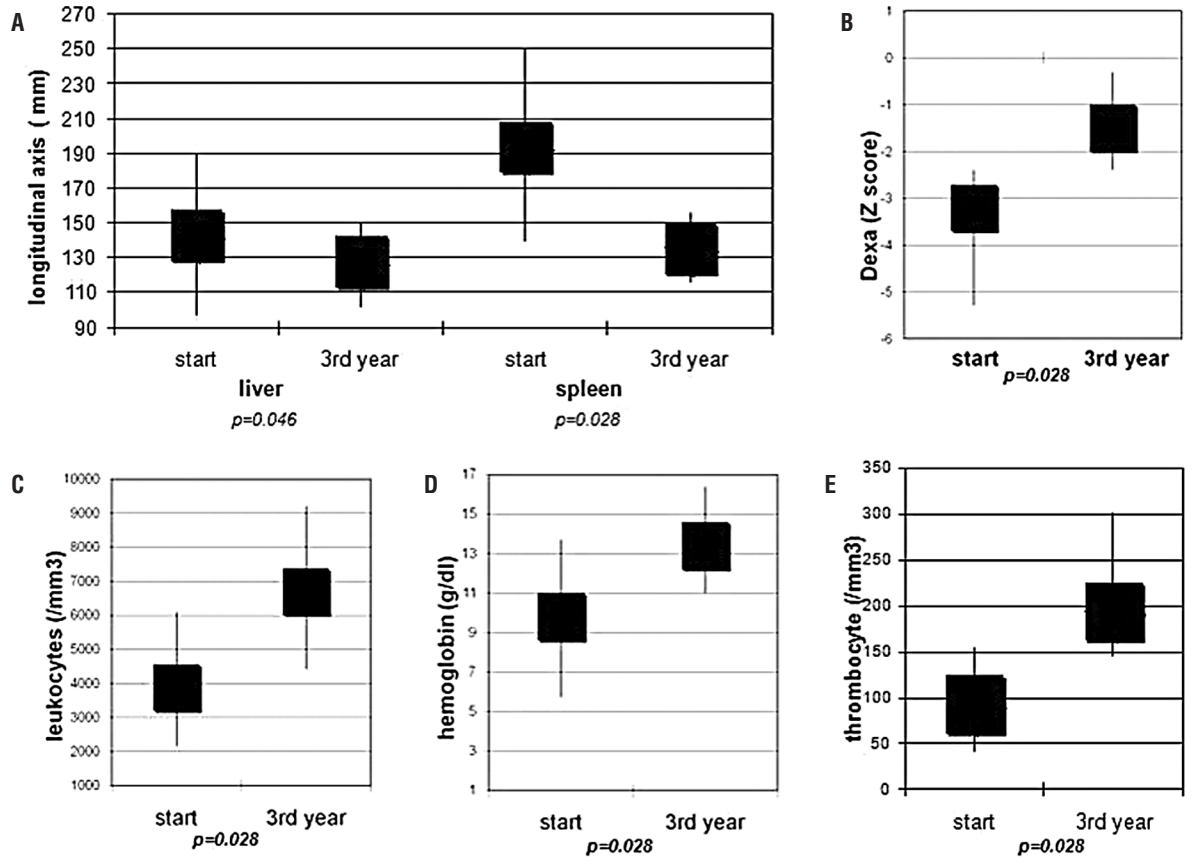

Figure 1. The comparison of A: ultrasonographic long axes of the liver and spleen; B: the changes in bone mineral density Z scores; C: the changes in leukocyte counts; D: the changes in hemoglobin levels; and E: the changes in thrombocyte counts, at baseline and at the third year of therapy.

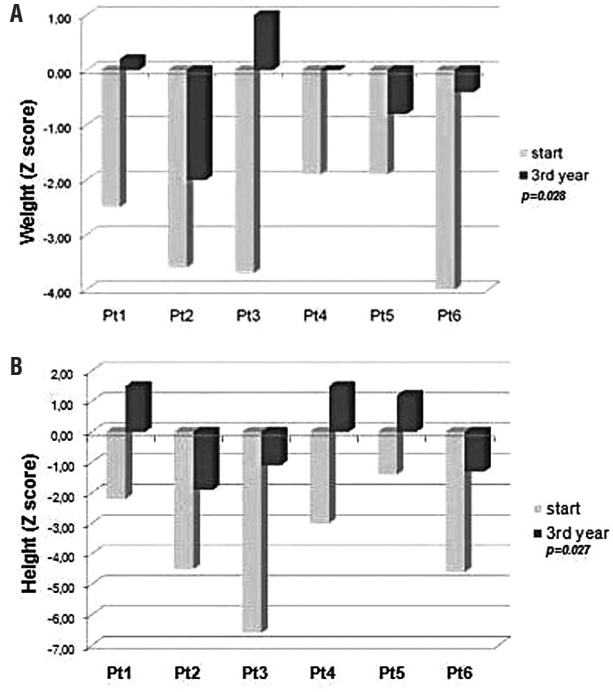

Figure 2. The changes in A: weight for age Z-scores; and B: the changes in height for age Z-scores, at baseline and at the third year of therapy.

sease. Genetic analysis revealed L444P homozygosity and confirmed the diagnosis. The dosage of imiglucerase was increased to 120 U/kg/ 2 weeks. No neurological deterioration occurred afterwards.

The other patient had been diagnosed as GD type 1 at the age of 7 years. Her parents were consanguineous and she had two cousins who died of type 2 GD. Her presenting symptoms were hepatosplenomegaly, anemia and thrombocytopenia. The neurological examination was normal. ERT could be started at the age of 12 years with a standard dose of imiglucerase (60 U/kg/2 weeks). After the second year of ERT, horizontal gaze palsy was detected on routine ophthalmologic examination. Her genetic analysis also revealed L444P homozygosity, and her diagnosis was changed to GD type 3a.

DISCUSSION

Diagnosis and management of inherited metabolic diseases is a common problem for countries in

which the consanguinity rate is high. GD, the most common lysosomal storage disease, is one of the well-understood metabolic disorders. With the availability of imiglucerase, physicians gained more experience in the management and follow-up of these patients.

Classically, a Gaucher type 1 patient has findings due to involvement of the liver, spleen and bone marrow. Failure to thrive, hypergammaglobulinemia, generalized lymphadenopathy, and pulmonary involvement are other rare findings of GD.

The phenotypic heterogeneity of Gaucher patients indicates the contribution of genetic and environmental factors on the course of the disease. The gene for GBA is localized to 1q21, and to date, over 250 mutations have been reported in GBA. A difference in the distribution in different populations is observed.

Mutations N370S, 84GG, L444P, and IVS+1G>A account for 90% of mutant alleles in Jewish populations, whereas they represent fewer than 75% of alleles in non-Jewish Caucasian patients. In a study including 57 unrelated Turkish patients, the most prevalent mutations were found to be N370S and L444P, accounting for 42% and 30% of patients, respectively (5).

Molecular analysis of GBA gene mutations is usually useful for predicting the severity and the prognosis of the patient (1). The N370S allele is known as the neuroprotective factor, and L444P allele is considered as an indicator of neuronopathic disease (5).

In our patient group, all type 1 patients had N370S allele and the other two patients with type 3 disease had L444P allele with homozygosity. Two rare mutations (6,7) (c.518C>T and c.1265_1319del) were detected in our two type 1 patients with compound heterozygosity with N370S. Due to the high consanguinity rate, the presence of novel or rare mutations is not surprising for our country.

The follow-up guidelines and therapeutic goals were developed in 2005 by the International Collaborative Gaucher Group. It is recommended to follow liver and spleen volumes with annual CT scans in GD (3). Considering the long life expectancy in Gaucher children, repeated CT scans will probably increase the risk of malignancy, in whom the risk is already high. Therefore, we preferred to follow our patients with serial abdominal ultrasonography, and obtained volumetric scan after the third year of ERT, when the liver and spleen sizes were already normalized in ultrasonographic measurements.

Type 3 Gaucher patients, particularly L444P homozygotes, usually present with non-neuronopathic symptoms and were usually mistakenly diagnosed as type 1 disease initially. Horizontal gaze palsy is usually seen as the first sign of neurological involvement (8). Therefore, neurological examination for abnormal eye movements must be done regularly for children diagnosed as GD during the first decade of life. Our two cases discussed above are quite clear examples of this scenario.

Enzyme replacement therapy (ERT) is indicated for the treatment of types 1 and 3 GD. Generally, the recommended dose of imiglucerase for children with type 1 disease is 60 U/kg body weight every two weeks (9). There are debates on the efficient dose for type 3 disease. Imiglucerase does not cross the blood-brain barrier, so even high doses of therapy are not expected to stop or reverse neurological symptoms (10). Since 2006, the same dose as for type 1 patients has been recommended for type 3 patients (1). In our patients, we preferred to continue with double dose (120 U/kg) because we observed the development of neurologic symptoms on standard dose imiglucerase.

The skeletal manifestations of GD progress slowly and become apparent in the teenage years (11). Medullary involvement in the femur and vertebra was common in all of our patients. Bone disease in three patients remained the same on ERT; however, the other three patients had deterioration: one developed vertebral collapse, one had intervertebral bulging and the third developed kyphosis. The occurrences of such kinds of bone lesions are unexpected in pediatric patients on ERT.

Bone mineral density (BMD) increase during the course of ERT was established previously. However, the improvement in BMD is usually expected after 4-8 years of ERT (9,12). This long period may be disadvantageous for growing children. In addition, competent bone formation may not be achievable after growth cessation. We achieved normalization of BMD in four patients with ERT, but antiresorptive therapy was needed in the other two patients who did not respond. We experienced the efficient use of bisphosphonates in refractory osteoporosis in pediatric patients.

Growth retardation is seen in half of pediatric Gaucher patients and most likely reflects the seve-

rity of the disease (13). Enzyme replacement leads to acceleration of growth and finally establishment of normal growth rates in children (13,14). We observed achievement of normal weight and height percentiles in all of our patients after the third year of ERT. Pubertal delay was not a problem for our patients and this may be attributed to the early start of ERT.

In conclusion, based on our experience, we can report remarkable points of childhood GD, such as late-onset neurological symptoms of type 3 patients and deterioration of vertebral bone lesions and pulmonary involvement despite ERT. Although GD is one of the well-managed metabolic diseases, new aspects are still needed to clarify the clinical course and therapy response in childhood.

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