JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.807622
J Contemp Med 2021;11(2):147-150

Orjinal Araştırma / Original Article

Gaucher Disease Type 1, A Rare Disease: A Single Center Experience

Gaucher Hastalığı Tip 1, Nadir Bir Hastalık: Tek Merkez Deneyimi

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Abstract

Aim: Gaucher disease is a rare lysosomal storage disease. Enzyme replacement therapy has proven to be very effective in reversing the risk of hepato-splenomegaly, cytopenia, osteopenia and reducing the risk of avasculer osteo necrosis, especially in children and young adults. The aim of this study is to draw attention to this rare disease and increase awareness.

Material and Method: All medical records of 8 patients diagnosed with Gaucher disease between 2008 and 2020 in our clinic were reviewed.

Result: Five of the cases were female (62.5%), average age at diagnosis; was 7.9 years. When complaints at the time of admission are examined, we found that, 3 patients admitted with swelling in the abdomen, one admitted with abdominal pain, and 4 patients had been referred to our center due to organomegaly detected during the examination. In physical examination 8 patient had splenomegaly. The mean level of glucocerebrosidase enzyme of the patients was found to be 0.61 mmol/l/h (normal range of glucocerebrosidase >3.2mmol/l/h). Considering the genetic analysis of the patients, 5 patients had homozygous and 3 patients had heterozygous mutations. One patient with portal hypertension who did not respond to enzyme replacement therapy at the time of admission underwent liver transplant.

Conclusion: Early diagnosis and treatment are important to live with in mind that this disease, which is rare in societies where consanguineous marriage is common and can result in serious morbidity and early death, can be seen more frequently.

Keywords: Rare diseases, lLysosomal storage disease, Gaucher disease, glucocerebrosidase

Öz

Amaç: Gaucher hastalığı, nadir görülen bir lizozomal depo hastalığıdır. Enzim replasman tedavisinin özellikle çocuklarda ve genç yetişkinlerde hepato-splenomegali, sitopeni, osteopeni riskini tersine çevirmede ve avaskular osteo nekroz riskini azaltmada çok etkili olduğu kanıtlanmıştır. Bu çalışmanın amacı, nadir görülen bu hastalığa dikkat çekmek ve farkındalığı artırmaktır.

Gereç ve Yöntem: Kliniğimizde 2008-2020 yılları arasında Gaucher hastalığı tanısı alan 8 hastanın tüm tıbbi kayıtları gözden geçirildi.

Bulgular: Olguların beşi kadın (%62,5), ortalama tanı yaşı; 7,9 yıldı. Başvuru anındaki şikayetler incelendiğinde; 3 hastanın karın bölgesinde şişlik ile başvurduğu, birinin karın ağrısı ile başvurduğu ve 4 hastanın muayene sırasında tespit edilen organomegali nedeniyle merkezimize sevk edildiği tespit edildi. Fizik muayenede 8 hastada splenomegali vardı. Hastaların ortalama glukoserebrosidaz enzim düzeyi 0.61 mmol/l/saat (normal glukoserebrosidaz aralığı >3.2 mmol/l/saat) olarak bulundu. Hastaların genetik analizine bakıldığında 5 hastada homozigot, 3 hastada heterozigot mutasyon vardı. Başvuru sırasında enzim replasman tedavisine yanıt vermeyen portal hipertansiyonlu bir hastaya karaciğer nakli yapıldı.

Sonuç: Ciddi morbidite ve erken ölümle bile sonuçlanabilen ve akraba evliliğinin sık olduğu toplumlarda nadir görülen bu hastalığın daha sık görülebileceği akla getirmek hastaların yaşam kalitesini arttırmak için erken tanı ve tedavi önem arz etmektedir.

Anahtar Kelimeler: Nadir hastalıklar, lizozomal depo hastalığı, Gaucher hastalığı, glukoserebrosidaz

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Received *(Geliş Tarihi)*: 09.10.2020 **Accepted *(Kabul Tarihi)*:** 17.01.2021

INTRODUCTION

Gaucher disease (GD) is a rare and chronic autosomal recessive lysosomal storage disease caused by GBA1 mutations characterized by glucocerebrosidase enzyme deficiency and accumulation of glucoceramide in the reticuloendothelial system. More than 400 mutations have been reported in the GBA1 gene.[1,2] The incidence of GD varies between 1:50,000 and 1: 100,000, and the frequency in Ashkenazi Jews is about 1: 855.[3] It was first described by Gaucher in 1882 and Braddy et al. determined that this disease was due to deficiency of a lysosomal enzyme called "β-glucocerebrosidase", in 1965. Hepatosplenomegaly, and bone fractures due to pancytopenia are common clinical findings in GD.

Although the diagnosis of the disease is based on the appearance of "Gaucher cells" (lipid-loaded macrophages in the bone marrow) in liver, spleen and bone marrow biopsies, since false gaucher cells can also be seen, the most reliable method is to show glucocerebrosidase activity in peripheral blood leukocytes.[4] It is classified under three types according to the degree, age of the patient, and findings: type 1 (chronic non-neuropathic type), type 2 (acute neuronopathic or infantile type), type 3 (subacute neuronopathic or juvenile type). In Type 1, hepatosplenomegaly, hypersplenism and skeletal pathologies are observed, whereas nervous system involvement is not observed. In Type 2, hepatosplenomegaly and hypersplenism are observed, but unlike Type 1, nervous system involvement occurs while bone fractures are not seen. In Type 3, hepatomegaly, hypersplenism, bone fractures and nervous system involvement are seen.[5] Type 1 is the most common form of the disease and constitutes 94% of all recorded GSD cases.[6] GD type 1 is a progressive disease that can result in damage, decreased quality of life, severe morbidity and even premature death. Especially in children and young adults, Enzyme Replacement Therapy (ERT) has proven to be highly effective in reversing hepatosplenomegaly, cytopenia, osteopenia and reducing the risk of avascular osteonecrosis.[7] Since Gaucher disease is a rare disease, the lack of consideration in the first evslustion may lead to diagnostic delays. The aim of this study is to draw attention to this rare disease and to increase awareness.

MATERIAL AND METHOD

This study was designed as an observational retrospective cohort and all medical records of 8 patients diagnosed with Gaucher disease between 2008 and 2020 at İnönü University Turgut Özal Medical Center Pediatric Gastroenterology, Hepatology and Nutrition Clinic were reviewed. Clinical and laboratory findings and the results of genetic analysis were collected. The study was approved by İnönü University Clinical Research Ethics Committee with protocol code 2020/978. Informed consent was obtained from the families of the patients.

Statistical Analysis

All data were summarized descriptively and statistical testing was not performed. Descriptive statistics for the categorical variables are presented by using mean and standard deviation (SD) and for continuous variables as percentage (%) and intervals.

RESULTS

Five of the evaluated cases were males (62.5%) and three were females (37.5%) and the mean age at diagnosis was calculated as 7.9 years. According to the complaints at the time of admission, 3 cases had abdominal swelling, one case had abdominal pain, and the other four cases were referred to our center after organomegaly was detected during the examination. Regarding the anthropometric measurements of the cases, the mean body weight Z score of the patients was -1.92, height Z score was 2.23, and body mass index Z score was -0.65. In the physical examination, 7 patients had hepatosplenomegaly and 1 patient had splenomegaly, in one of the patients with hepatosplenomegaly migratory spleen was present. The patient with a migratory spleen had admitted with abdominal pain. In 5 (62.5%) of the cases, there was cytopenia in the complete blood count at the time of admission. In the family history of the cases, 5 patients were inbred of consanguineous marriage. Gaucher cells were observed in bone marrow aspiration in 4 of the patients. in one of these patients who was 8-month-old, liver biopsy was performed and in addition to the appearance of Gaucher cells in bone marrow aspiration, sinusoidal and portal area histiocytic cell groups compatible with Gaucher disease were observed in liver biopsy. When the glucocerebrosidase enzyme levels of the patients were examined, it was seen that the enzyme level was zero in 3 patients and the enzyme levels were significantly below normal in other 5 patients. The mean glucocerebrosidase enzyme level of 8 patients was found to be 0.61 mmol/l/h (normal range is >3.2 mmol/l/h). When the genetic analyzes of the patients were examined, it was seen that 5 patients had homozygous mutations and the other 3 patients had heterozygous mutations. DEXA (dual energy X-Ray absorptiometry) evaluation was performed in 5 patients at the time of admission to see bone mineral density and ranged between -2 and -5. The clinical characteristics of the patients were shown in **Table1**.

In 6 patients diagnosed with Gaucher disease, enzyme replacement therapy (imigluserase) was initiated at a dose of 30 IU/kg/dose depending on the clinical findings and in two patients at a dose of 60 IU/kg, because platelet was 50000/mm3 and Hb was less than 8 g/dl.

Enzyme replacement therapy dose was revised according to the status of the patients in the follow-up. In the follow-up, it was observed that organomegaly improved in 3 patients in 1 year and in 1 patient in 4 years. One of the patients underwent liver transplantation because the signs of portal hypertension detected at the time of admission did not regress during the follow-up despite enzyme replacement therapy. In addition, in 3 of 5 cases whose bone mineral density was evaluated by DEXA method at the time of first admission, significant improvement was observed after enzyme replacement therapy.

Table 1. Clinical propeties of the patien

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age of diagnosis	15 months	14 years	23 months	6 years 9 months		10 years 6 months	8 months	14 years 10 months
Gender	F	F	M	M	F	F	M	F
Subcostal liver measurement at admission	6 cm	4 cm	5 cm	2 cm	4 cm	6-7 cm	2 cm	NP
Subcostal spleen measurement at admission	16 cm	13 cm	10 cm	6 cm	12 cm	9 cm	10 cm	5-6 cm
History of consanguinity	+	+	-	-	+	+	+	-
Cytopenia at admission	+	-	-	-	+	+	-	+
Storage cell in bone marrow	+	-	+	+	-	-	+	-
Liver biopsy	-	-	-	-	-	-	Compatible with Gaucher Disease	-
Enzym level mmol/l/h (>3,2 mmol/l/h)	0	1,9	0	0	1,54	0,2	0,1	1,2
DEXA (Z score)	-5	-	-2	-	-3	-2	-	-4
Genetics	Homozygote c.[1193G>T]; 1193G>T]	Heterozygote c.[1265_1219del]; [1342G>C]	Homozygote c.[148T>C]; c[148T>C]	Heterozygote c.[1226A>G];. [1448T>C; 1497G>C]	Homozygote c.[1193G>T]; 1193G>T]	Homozygote c.[1214G>C]; [1214G>C]	Homozygote c[148T>C]; c[148T>C]	Heterozygote [1448T>C; 1497G>C]
Treatment	30 unit/kg	30 unit/kg	30 unit/kg	30 unit/kg	60 unit/kg	30 unit/kg	30 unit/kg	60 unit/kg
Duration of treatment (years)	5	5	5	8	12	3	5	4
Subcustal liver measurement after treatment	4 cm	NP*	NP*	NP*	NP*	2 cm	NP*	Liver transplantation
Subcustal spleen measurement after treatment	10 cm	Splenectomy	NP*	NP*	NP*	NP*	NP*	Liver transplantation
DEXA after treatment	-2,2	-	-1.1	-	-2	-1	-	-4

*:Non palpabl

DISCUSSION

Gaucher disease is the most common lysosomal storage disease and affects many systems. Splenomegaly, hepatomegaly, skeletal pathology, growth retardation and pulmonary disease develop in Type 1 GD is non-neuronopathic and leads to a decrease in quality of life. Anemia and thrombocytopenia are seen due to hypersplenism. Glucoceramide accumulation in the bone marrow is associated with osteopenia, pathological fractures, lytic lesions, chronic bone pain (bone crisis) and osteonecrosis. Although anemia and thrombocytopenia can be severe, the greatest cause of morbidity is often bone disease resulting in long-term disability.

ERT should be initiated immediately after diagnosis of type 1 Gaucher disease in children and should be continued to improve the severity of the disease and to prevent complications, particularly the development of irreversible bone disease.[8] For this reason, in patients admitted to pediatric hepatology, pediatric hematology, pediatric pulmonary diseases, and orthopedics outpatient clinics, GD, which is rarely seen should be considered in the diagnosis. Early diagnosis of the disease is important for reducing morbidity and improving quality of life.

Hepatomegaly; defined as a liver, which is in excess of 2.5% of body weight and is 1.25 times larger than the normal volume of the liver.[9] Hepatomegaly is one of the most common symptoms in GD and often causes abdominal pain and a slight increase in transaminases.[10] In addition, patients with cholelithiasis, hemosiderosis steatosis, focal fibrosis, portal hypertension, cirrhosis, and hepatocellular carcinoma (HCC) have been reported.[11] Patlas et al.[12] reported a 100% prevalence of hepatomegaly in a cohort of 103 pediatric patients, by ultrasound. In three of our cases, there was abdominal distension at the first presentation and one case had abdominal pain. The other four cases had been referred to our center due to the detection of organomegaly during the examination. Seven of our patients had hepatomegaly on physical examination, and only splenomegaly was present in one patient with portal hypertension. In Gaucher disease liver fibrosis has rarely been reported.[13] In a series of 53 patients, portal hypertension complications have been reported only in

two patients.[14] In patients with hepatic parenchymal disease, ERT may be insufficient to prevent progression to hepatic decompensation.[15] In our series 1 patient underwent liver transplantation because of symptoms of portal hypertension and his findings did not regress in the follow-up despite enzyme replacement therapy. Pathological analysis of the explanted liver showed that it was compatible with cirrhosis. Liver transplant is a life-saving treatment for end-stage liver disease in patients with Gaucher disease. Ayto et al. in their report of the results of liver transplantation in four patients with GD and end-stage liver disease, reported that all patients had excellent results after liver transplantation up to 10 years post-procedure, without evidence of Gaucher-associated pathology in the graft.[15] Our patient has been followed up for 5 years, after the transplantation, without any problem.

In the assessment of bone mineral density at the time of first admission, the DEXA Z score of 5 patients was between -2 and -5. After ERT, the DEXA Z score of 3 patients returned to normal and a significant improvement was observed in 2 cases.

CONCLUSION

Gaucher disease develops as a result of glucocerobrosidase enzyme deficiency. It is a rare, autosomal recessively inherited lipid storage disease that is characterized by the accumulation of glucocerobroside in reticuloendothelial system cells. This rare disease is seen more frequently in societies where consanguineous marriage is common and can cause serious morbidity and early death. Early diagnosis and treatment are important in order to improve the quality of life of patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Local Ethics Committee of Inonu University (approval number: 2020/978).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES:

1. Nguyen Y, Stirnemann J, Belmatoug N. La maladie de Gaucher: quand y penser ?.[Gaucher disease: A review] Rev Med Interne. 2019;40(5):313-322. doi:10.1016/j.revmed.2018.11.012
2. Nalysnyk L, Rotella P, Simeone JC, Hamed A, Weinreb N. Gaucher disease epidemiology and natural history: a comprehensive review of the literature. Hematology. 2017;22(2):65-73.
3. Starosta RT, Vairo FPE, Dornelles AD, et al. Liver involvement in patients with Gaucher disease types I and III. Mol Genet Metab Rep. 2020;22:100564. doi:10.1016/j.ymgmr.2019.100564
4. Beutler E, Saven A. Misuse of marrow examination in the diagnosis of Gaucher disease. Blood. 1990;76(3):646-8
5. Dandana A, Ben Khelifa S, Chahed H, Miled A, Ferchichi S. Gaucher Disease: Clinical, Biological and Therapeutic Aspects. Pathobiology 2016;83:13-23.
6. Cox TM. Gaucher disease: clinical profile and therapeutic developments. Biologics. 2010;4:299-313.
7. Mistry PK, Deegan P, Vellodi A, Cole JA, Yeh M, Weinreb NJ. Timing of initiation of enzyme replacement therapy after diagnosis of type 1 Gaucher disease: effect on incidence of avascular necrosis. Br J Haematol. 2009;147(4):561-70.
8. Zimran A, Hadas-Halpern I, Zevin S, Levy-Lahad E, Abrahamov A. Low-dose high-frequency enzyme replacement therapy for very young children with severe Gaucher disease. Br J Haematol. 1993;85(4):783-6.
9. Pastores G. M, Weinreb N. J, Aerts H. et al. Therapeutic goals in the treatment of Gaucher disease. In Seminars in hematology. 2014; 41:4-14.
10. Zimran A, Elstein D, Levy-Lahad E, et al. Replacement therapy with imiglucerase for type 1 Gaucher's disease. Lancet 1995;345(8963):1479-80.
11. Adar T, Ilan Y, Elstein D, Zimran A. Liver involvement in Gaucher disease–Review and clinical approach. Blood Cells Mol Dis 2018;68:66-73.
12. Patlas M, Hadas-Halpern I, Abrahamov A,. et al. Spectrum of abdominal sonographic findings in 103 pediatric patients with Gaucher disease. Eur Radiol 2002;12(2):397-400
13. James SP, Stromeyer FW, Chang C, Barranger JA. Liver abnormalities in patients with Gaucher's disease. Gastroenterology. 1981;80(1):126-33
14. Zimran A, Kay A, Gelbart T. et al. Gaucher disease. Clinical, laboratory, radiologic, and genetic features of 53 patients. Medicine1992;71:337–53.
15. Ayto RM, Hughes DA, Jeevaratnam P, et al. Long-term outcomes of liver transplantation in type 1 Gaucher disease. Am J Transplant. 2010;10(8):1934-9.