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Gaucher Disease Incidence in Patients with Splenomegaly, Hepatomegaly and/or Thrombocytopenia

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Abstract

Aim: Gaucher disease is the most common Lysosomal Storage Disease (LSD). Although the incidence of GH is 1/40,000-1/60,000, it is more common especially in Ashkenazi Jews. GH can be seen in one person out of 450 in this community. GH is an autosomal recessive disease. Because consanguineous marriages are high in Turkey, the incidence of autosomal recessive diseases is also high. In local studies, the incidence in our country has been determined as 2.3/1,000,000. Patients are usually diagnosed in childhood. However, there are also adult patients whose diagnosis is delayed because the symptoms are not obvious and they are not evaluated in terms of metabolic disease. This study was planned to emphasize the importance of the need for evaluation in terms of metabolic diseases in patients who were examined for etiology due to hepatomegaly, splenomegaly and/or thrombocytopenia findings.

The aim of our study is to consider Gaucher's disease in adult patients with findings such as splenomegaly, hepatomegaly and/or thrombocytopenia, which are common reasons for admission to internal medicine outpatient clinics.

Materials and methods: The study was planned as a retrospective, single center study. 91 people (47 women, 44 men) who applied to Ankara city hospital internal diseases polyclinics between 2020-2022 and were investigated for splenomegaly (>12 cm), hepatomegaly (>14 cm) and/or thrombocytopenia (plt<150.000/mm^3) findings) was included.

Results: 91 cases with hepatomegaly, splenomegaly and/or thrombocytopenia who met the inclusion criteria were included in our study. Glucocerebrosidase enzyme level was normal in 79 patients (86.8%); beta glucosidase enzyme level was found to be low in 12 patients (13.2%). Mutation analysis was performed in patients with low enzyme levels. Mutation was detected in 3 (25%) of 12 patients with low enzyme levels. These patients were considered to have Gaucher disease. No mutation was detected in the other 9 patients (75%). As a result of our study, one of the 3 patients who were accepted as GH was able to receive enzyme replacement therapy. We lost our other two patients due to complications related to GH at the time of diagnosis.

Conclusion: Gaucher is a condition that can be easily diagnosed as long as there is sufficient awareness, and although it cannot be completely eliminated, a significant reduction in mortality and morbidity will be achieved with replacement therapies.

Keywords: Gaucher disease; b-glucosidase; Splenomegaly; Thrombocytopenia

Introduction

Gaucher disease is a relatively common lysosomal storage disease caused by mutations in the GBA gene, located on chromosome 1 (1q21) [1]. It results in deficiency of glucocerebrosidase and leads to an accumulation of glucosylceramide in macrophages. The phenotype of GD is variable, including splenomegaly, hepatomegaly, cytopenia, bone involvement and/or neurological impairment. Depending on the presence of neurological involvement and disease progression, GD can usually be classified into three clinical subtypes, which are type 1, the non-neuronopathic form; type 2, the acute neuronopathic form; and type 3, the subacute neuronopathic form (1-2-3). The incidence of GD is diverse invarious ethnic populations. The GD prevalence in the general population varies between 0.4 and 5.8 per 100,000. Type 1 disease is the most prevalent form in the Western world (US, Europe, Israel and other European-derived Caucasian populations), accounting for ~94% of patients [2]. Types 2 and 3 are neuronopathic variants representing, 1% and 5% of patients, respectively, in Europe, North America, and Israel. Types 2 and 3 have much greater frequencies in "non-western" countries including non-Israeli Middle East, Indian subcontinent, China, Japan, and Korea.

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GD and similar genetic metabolic diseases are more prevalent in regions in which consanguineous marriages are frequent, as in the Ashkenazi Jewish population [3]. There are studies showing that this prevalence is higher due to the frequency of consanguineous marriages in Turkey.

Patients are usually diagnosed in childhood. However, there are also adult patients whose diagnosis is delayed because the symptoms are not obvious and they are not evaluated in terms of metabolic disease [4]. Early diagnosis is important for starting proper treatment and preventing complications as well as disease progression [5]. Because Gaucher is a condition that can be easily diagnosed as long as there is sufficient awareness, and although it cannot be completely eliminated, a significant reduction in mortality and morbidity will be achieved with replacement therapies.

Description

The study was planned as a retrospective, single center study. 91 people (47 women, 44 men) who applied to Ankara city hospital internal diseases polyclinics between 2020-2022 and were investigated for splenomegaly (gt; 12 cm), hepatomegaly (gt; 14 cm) and/or thrombocytopenia (plt and lt; 150.000/mm^3) findings) was included [6].

Labaratuar test: For the enzymatic diagnosis method, blood samples were taken from the patients included in the study. The study was performed by means of tandem mass spectrometry from DBS obtained by dripping blood. GBA activity in leukocytes was measured with an artificial fluorogenic substrate 4-methyl-umbelliferyl-β-glucopyranosyl. Leukocytes were isolated from fresh heparinized blood. The substrate was added to 0.2 mol l^{-1} citrate-phosphate buffer (pH 5.8 containing 0.3% sodium taurocholate and 0.15% Triton-X 100) to obtain a final concentration of 5 mmol l^{-1}. 20 µl substrate and 10 µl homogeneous mixture were incubated at 37°C for 2 hours [7]. Then, 200 µl of glycine carbonate buffer (0.17 mol l^{-1}, pH 10.5) was added to stop the reaction. Fluorescence was measured (excitation 355 nm, emission 460 nm) and GBA activity expressed as nmol h^{-1} per mg protein. Enzymatic activity was expressed as micromoles of 4-MU hydrolyzed substrate per liter of blood per hour. Suspicious results were retested in duplicate. Positive cases were confirmed by GBA activity in leukocytes and *GBA* gene analysis. For molecular screening, *GBA* gene mutation analysis was performed using NGS (Illumina® NextSeqTM 550Dx) in patients with low leukocyte β-GBA and borderline (<=1 nmol/mg/hr). Specific PCR primers were used to distinguish the *GBA* gene from its pseudo genes.

Statistical analysis: Statistical evaluations were performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL) program. Numerical variables showing normal distribution were shown as mean ± standard deviation and numerical variables not showing normal distribution were shown as median (minimum, maximum) [8]. Categorical variables were expressed as numbers and percentages. *Chi-square* and Fisher's exact *Chi-square* test were used to compare categorical data. The student T test or Mann Whitney U test was used to compare the variables between the two groups according to the normality distribution. A $p<0.05$ (*) value was considered significant in statistical analysis.

Our study included 91 patients (mean age 44.97 ± 1.39 years), 44 male (49.4%) and 47 female (51.6%). Among all patients, 64 (70.3%) hepatomegaly, 68 (74.7%) splenomegaly, and 10 (11%) cirrhosis were detected. 13 (14.3%) patients have fractures and in 60 (65.9%) patients bone pain, bleeding in 65 (71.4%) patients, and abdominal pain in 25 (25.3%) patients were detected. Among these patients, 79 (86.8%) had normal GBA levels and 12 (13.2%) had low GBA levels. 12 patients with low GBA levels were recalled and genetic confirmation was given to three (25%) of these patients. Mutation was detected. Of the 3 patients with mutation, 2 (75%) were male and 1 (25%) was female, and the mean age was accepted as 64 ± 18 GH. Disease was excluded in the other 9 patients.

Glucocerebrosidase enzyme level was normal in 79 patients (86.8%). Therefore, 3 of 91 patients have been diagnosed with GD, with a prevalence of 3.2% in this selected population [9]. Among them, 2 patients (1 female and 1 male) had hepatosplenomegaly, 1 patients had only splenomegaly. All three patients had thrombocytopenia.

In the subgroup analysis, the group with low GBA enzyme level had higher total cholesterol and LDL levels than the group with normal GBA enzyme level (total cholesterol $p=0.014$) and LDL $p=0.01$)

Conclusion

Although rare, GD is the most common autosomal recessive lysosomal storage disorder due to defects of the *GBA1* gene encoding for the b-glucosidase enzyme or delay their diagnosis. The most common symptoms in GH are splenomegaly and/or thrombocytopenia. After excluding common causes in adult patients presenting with splenomegaly, hepatomegaly, thrombocytopenia, which we frequently encounter in clinical practice, we should also exclude Gaucher's disease.

Although the incidence of Gaucher disease is 1/40,000-1/60,000, it is more common especially in the Ashkenazi community. According to the studies of Ozkara, et al., the incidence of the disease in Turkey was determined as 2.3/1,000,000. In the study of Yanardag Acik Dindar, et al., in Adana, the frequency of GD was determined as 23/100 000.

Our study included 91 patients who applied to Ankara Bilkent city hospital and were found to have unexplained hepatomegaly, splenomegaly and/or thrombocytopenia and 3 of these patients were diagnosed with GH. Only one of these patients could be treated. The other two patients were diagnosed with sepsis; esophageal avarices as the cause of bleeding. It is vital that the diagnosis of patients is not delayed. Enzyme replacement therapy has been reimbursed since 2004 in Turkey, and patients diagnosed with GH are being treated. Although long-term use of ERT is thought provoking in terms of cost, when the complications that can be prevented by enzyme replacement therapy are taken into account, it can be seen that there is no significant difference in the total cost.

Stirnemann, et al. type 1 GH observed increased triglyceride levels and decreased HDL-cholesterol and ApoA1 levels. In our study, it was observed that total cholesterol and LDL levels were high in patients with GH. For this reason, when investigating the etiological causes of findings such as hepatomegaly, splenomegaly and cytopenia, Gaucher's disease, which can be diagnosed with a simple approach due to other common causes, should definitely be considered. As a result, Gaucher is a disease that can be easily diagnosed as long as there is sufficient awareness. Although it cannot be completely eliminated, it is a condition in which fatal complications can be prevented with replacement therapies.

As a result of our study, although we cannot specify the general incidence, we see that this rate is 3/91 in the limited number of specific patients we have performed in our hospital. This makes us think that GH that can be diagnosed in adulthood may be higher. As a result, a larger population study is needed to calculate the incidence across Turkey.

Ethical Consideration

This study was approved by the Ankara city hospital no. 2 clinical research ethics committee on 24/11/2021 with the document numbered E2-21-1055.

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