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Orjinal Araştırma / Original Article

Prevalence of Gaucher's Disease in a Hematology Outpatient Clinic

Hematoloji Polikliniğinde Gaucher Hastalığı Sıklığı

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Abstract

Objective: Gaucher's disease (GD) is a disease caused by glucocerebrosidase enzyme deficiency and characterized by glucoceramide accumulation in the reticuloendothelial system. In this study, we aimed to determine the prevalence of GD in patients who were diagnosed with GD in a hematology clinic.

Method: The diagnoses of 26,000 patients who had applied to the hematology polyclinic between 2014 and 2018 were examined retrospectively. The number of patients diagnosed with GD was compared to the number of total patients and the number of patients with hepatosplenomegaly diagnosis. The results were recorded as ratios.

Results: The prevalence of GD was found as 23/100,000 in our study. It was found that splenomegaly was present in almost all of the diagnosed cases of GD. The thrombocyte levels of patients with splenomegaly were low.

Conclusion: GD is not as rare as is claimed in the literature, especially in people living in regions in which consanguineous marriages are common. Both clinicians and pathologists should be reminded that patients with diagnosed hepatosplenomegaly and thrombocytopenia need to be investigated with regard to lysosomal storage diseases.

Keywords: Gaucher's disease, hepatomegaly, lysosomal storage disease, splenomegaly, thrombocytopenia

Öz

Giriş: Gaucher hastalığı (GD) glukoserebrosidaz enzimi eksikliği sonucu meydana gelen ve retiküloendotelyal sistemde glukozilseramid birikimi ile karakterize bir hastalıktır. Bu çalışmada hematoloji polikliniğinde GD tanısı konulan hastalarda GD sıklığını belirlemeyi amaçladık.

Yöntem: 2014-2018 tarihleri arasında hematoloji polikliniğine başvuran 26 000 hastanın retrospektif olarak tanıları incelendi. Gaucher hastalığı tanısı alan hastaların sayısı toplam hasta ve hepatosplenomegali tanısı olan hastalarla karşılaştırıldı. Sonuçlar oransal olarak kaydedildi.

Bulgular: Çalışmamızda GD sıklığı 23 / 100 000 olarak saptandı. GD tanısı konulan vakaların hemen hemen hepsinde splenomegalinin var olduğu saptandı. Splenomegalisi olan vakaların trombosit düzeyleri düşük gözlendi.

Sonuç: Sonuç olarak GD, özellikle akraba evliliklerinin fazla olduğu bölgelerde yaşayanlarda literatürdeki kadar nadir değildir. Hepatosplenomegali ve trombositopeni saptanmış olguların lizozomal depo hastalıkları açısından da araştırılması gerektiği hem klinisyenlere hem de patologlara hatırlatılmalıdır

Anahtar Sözcükler: Gaucher hastalığı, hepatomegali, lizozomal depo hastalığı, splenomegali, trombositopeni

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INTRODUCTION

Gaucher's disease (GD) is a disease caused by glucocerebrosidase enzyme deficiency and characterized by glucoceramide accumulation in the reticuloendothelial system.[1] Clinically, there are three types: Type 1, the chronic non-neuronopathic type; Type 2, the acute infantile neuronopathic type; and Type 3, the juvenile or subacute neuronopathic type.[2] GD mainly accompanies pancytopenia, hepatosplenomegaly, and bone deformities. In Type 3 GD, there are central neural system symptoms in addition to organ involvement.[3]

Delays are frequent in GD diagnosis and these delays are mostly due to the lack of awareness of the disease. Irreversible complications occur in patients due to these delays, and the patients undergo unnecessary invasive procedures.[4,5] GD and similar genetic metabolic diseases are more prevalent in regions in which consanguineous marriages are frequent, as in the Ashkenazi Jewish population.[3] The Çukurova region of Turkey has received migrants from the eastern and southeastern provinces of the country. Research indicates that the rate of consanguineous marriages reaches 40.4% in these regions, while the frequency of consanguineous marriage is 20.9% in the entire country.[6,7] Therefore, the prevalence of GD in the Çukurova region is anticipated to be higher when compared to the national population.

The GD prevalence in the general population varies between 0.4 and 5.8 per 100,000.[8] We could not identify any comprehensive study on GD prevalence in Turkey, and there are also no studies with that purpose conducted in the Çukurova region. Therefore, in this study we aimed to determine GD prevalence in patients diagnosed with GD in a hematology polyclinic.

MATERIAL AND METHOD

A total of 26,000 patients who had applied to the hematology clinic between 2014 and 2018 were included in the study. The beta-glucosidase enzyme was checked in retrospective screenings, and patients were identified who had received a diagnosis of GD with the mutation test after their enzyme levels were found to be low. Clinical characteristics and laboratory test results of the GD patients were recorded from their files.

Patients whose glucosidase enzyme levels were normal or who were not found to be abnormal in the mutation tests were not considered as having GD.

Approval for the study was obtained from the University Faculty of Medicine Ethical Committee in line with the Helsinki Declaration criteria, revised in Brazil in 2013.

Statistical Analysis

Statistical evaluations were conducted using SPSS 20 for Windows (IBM SPSS Inc., Armonk, NY, USA). The normal distribution of the data was tested with the KolmogorovSmirnov test. Normally distributed numerical variables are presented as average ± standard deviation, and nonnormally distributed variables are presented as median (minmax). Categorical variables are presented as numbers and percentages.

RESULTS

Table 1 presents the detailed clinical and demographic findings of the patients diagnosed with GD. During the screening of patients who had been referred to our clinic because of cytopenia or hepatosplenomegaly, six were diagnosed with GD and one with Niemann-Pick disease. The GD prevalence in the patients who had applied to our polyclinic was found to be 23/100,000. In five of the GD patients, splenomegaly was found. One patient was found to have had splenectomy due to splenomegaly. Thrombocyte levels for all patients, except for the one who had undergone splenectomy, were low. The youngest patient was 25 years old and the oldest patient was 59 years old. The patient with the earliest diagnosis had received the diagnosis with a 25-year delay. When we examined the physicians' notes in the patients' files, we found that patients were recommended to undergo a family screening, but the patients and/or their relatives had not followed this recommendation.

Table 1. Clinical and demographic characteristics of Gaucher patients

Gender	Age (years)	Type	HB (g/dL)	MCV (fL)	WBC (103µ)	PLT (103µ)	Spleensize (mm)	Liversize (mm)
Male	40	Type3	14	82.6	4.48	66000	220	Normal
Female	59	Type1	13.4	90.1	5.4	83000	180	Normal
Female	46	Type1	11.8	81.4	4.4	66000	165	180
Male	38	Type3	15	88.5	16.5	247000	Splenectomy	Normal
Female	25	Type1	11.7	78.3	4.8	77000	170	200
Female	52	Type1	12.1	88	5.6	55000	200	162

DISCUSSION

This is the first study to determine the prevalence of GD in the Çukurova region in Turkey. The GD prevalence was found to be 23/100,000 in our study. Splenomegaly was found in almost all of the diagnosed cases of GD. Thrombocyte levels were found to be low in the patients with splenomegaly.

GD is among the rare diseases in the literature and its awareness among clinicians is very low. Therefore, there are delays in diagnosis in patients who apply with different findings and symptoms. When the disease appears before the clinician with severe findings and symptoms in childhood, the odds of a diagnosis may be higher. However, since awareness is low in cases that progress with mild symptoms and findings, and with slowly developing hepatosplenomegaly, pancytopenia, and kidney pathologies in adults, delays might occur in diagnosis. Indeed, some patients continue their lives with multiple organ dysfunction without receiving any diagnosis. The GD prevalence in the general population varies between 0.4 and 5.8 per 100,000.[8] In our study, this ratio was found to be much higher. There could be two distinct reasons for this difference. First, our hospital is a large center, treating patients who could not be diagnosed in the peripheral hospitals in the region and who require a multidisciplinary approach. This could be the reason for the GD prevalence to be found higher. A second possible reason is that consanguineous marriages are very frequent in Adana province, which has received migrants in great numbers from the eastern and southeastern provinces of Turkey. GD is a genetic and metabolic disease, the prevalence of which increases with consanguineous marriage. Since GD is a genetic disease, family screenings should be done immediately after diagnosis. The elder sister of the 25-year-old patient whom we had diagnosed with Type 1 GD had undergone a liver transplantation; a reason for liver failure could not be found and the sister died. Despite this, consent for family screenings could not be obtained from the families of the patients we diagnosed with GD. We believe there are several reasons for this. We think that the most basic reason is that the socioeconomic levels of the people living in the region are very low. This brings about concerns that their family is a "diseased" one and that their children of marrying age would face the risk of refusals, as well as concerns about increasing hospital expenses and difficulty in accessing higher levels of healthcare centers. To solve these problems, the patients and their relatives should receive comprehensive genetic guidance, and economic burdens should not be imposed upon them during the diagnosis and treatment stages.

The failure to diagnose GD patients, in spite of the fact that they apply to hospitals many times and are referred to many departments, causes psychological fatigue, reduced confidence in physicians, and lower quality of life due to complications.[9-11] In addition, this lack of diagnosis may cause unnecessary invasive procedures such as splenectomy and costly extreme or even fatal treatments such as transplantations when organ failure occurs (e.g., cirrhosis of the liver). For instance, a 40-year-old patient diagnosed with Type 3 GD had started combined antiepileptic treatment with an epilepsy diagnosis; the dosages and combinations of the medications had been increased due to increasing epileptic seizures, but it had not been identified that the underlying reason was Type 3 GD. Likewise, a 38-year-old male patient diagnosed with Type 3 GD had undergone splenectomy due to splenomegaly and thrombocytopenia; however, the reason for splenomegaly could not be clarified. The failure to diagnose GD despite splenectomy indicates that pathologists, in addition to clinicians, do not think of lysosomal storage diseases and do not conduct examinations from this perspective. In a study that included 12 countries, it was concluded that the delays in diagnosis were mostly due to lack of awareness of the disease. In the same study, it was found that GD is diagnosed in hematology clinics the most.[4] In our center, all patients were diagnosed in the hematology clinic, in line with the literature.

Our main limitation is that our study is a retrospective one. Therefore, we believe that there might be patients remaining undiagnosed since different genetic examinations were not conducted although they had applied to our clinic and had undergone detailed screenings; there might be numerous genetic mutations in GD and we could examine only a portion of these. Another limitation is that the study was conducted in a single center in the region. This limitation might cause the real prevalence to not be reflected.

In conclusion, GD is not as rare as is claimed in the literature, especially in people living in regions in which consanguineous marriages are common. Both clinicians and pathologists should be reminded that patients diagnosed with hepatosplenomegaly and thrombocytopenia also need to be investigated with regard to lysosomal storage diseases.[5] It might be necessary to call family practitioners' attention to this issue as well, and to provide them with the means to conduct research on this disease. This would make it possible to reach a wider population and prevent delays in diagnosis. Patients should also be informed about the risks of consanguineous marriages and the occurrence of new cases should be prevented.

ETHICAL DECLARATIONS

Ethics Comittee Approval: Approval for the study was obtained from Çukurova University Faculty of Medicine Ethical Committee with the decision number: 91, dated: 2019.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Status of Peer-review: Externally peer-reviewed.

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

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