



# Viral respiratory tract infection in Gaucher disease, a rare disease: A case study of 24 patients in Malatya, Türkiye

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## Abstract

**Aim:** People with chronic diseases have a higher rate of morbidity and mortality from SARS-CoV-2 infection. Unknown is how SARS-CoV-2 affects rare disease populations like Gaucher disease. The purpose of this research was to investigate the effects of SARS-CoV-2 infection has on Gaucher patients. The only study conducted in Turkey so far is this one.

**Materials and Methods:** Patients with Gaucher disease were included in the study between August 2020 and September 2022. Patients diagnosed with Gaucher disease were questioned one-on-one to determine if they had come into contact with another person who had COVID-19 symptoms or another patient who had COVID-19. The patients were questioned and their answers were recorded regarding their GBA genotype, previous splenectomy history, whether or not they received treatment, and whether or not they had a SARS-CoV-2 test.

**Results:** Eight of our patients reported having contact with someone who had COVID-19 infection or was suspected of having the infection, and in three of these cases (37.5%) the patient reported having at least one symptom of infection. Out of the 18 patients who were tested, 4 (22.2%) had a positive result. Positive test results were associated with more symptoms in patients (3.8 vs 0.3, p0.001) than negative test results. In Gaucher patients, symptoms or positive test results were not correlated with age, gender, BMI, comorbidity, genotype, previous splenectomy, or enzyme replacement therapy. All of our patients only received supportive care; none of them required intensive care or specialized treatment.

**Conclusion:** Our research revealed that there was a low risk of serious side effects in other chronic patients following SARS-CoV-2 infection in Gaucher patients. In this regard, studies with larger case series are required.



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## Introduction

Infection with SARS-CoV-2 is associated with high morbidity and mortality in people who already suffer from chronic diseases [1]. Patients with lysosomal and other metabolic disorders were thought to be at a higher risk of poor disease outcomes and death from the SARS-CoV-2 virus when the novel coronavirus disease 2019 (COVID-19) pandemic first started. This was the consensus of the community that studies rare diseases [2].

The lysosomal storage disease known as Gaucher is extremely uncommon. Chronic myeloid cell immune activation is caused by Gaucher disease, which is characterized

by a reduction in acid -glucosidase activity and an accumulation of inflammatory glycosphingolipids in the body [3]. It is not known how SARS-CoV-2 will affect patients suffering from rare disease groups like Gaucher disease. The activation of the immune system's myeloid cells in patients with Gaucher disease is a strong indicator that the effects of this infection will be severe [1, 4].

COVID-19 has a severe course in patients suffering from certain chronic diseases because the immune system is compromised in these conditions; as a result, significant morbidity and mortality are caused [5]. It is unknown to what extent it contributes to the progression of rare diseases such as Gaucher's disease. The autosomal recessive form of the lysosomal storage disease known as Gaucher disease [6]. The absence of the glucosidase enzyme causes an accumulation of inflammatory glycosphingolipids, including glucocerebroside and glycosylsphingosine, which

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ultimately results in disease [7]. Patients with Gaucher disease often have complex multisystemic involvement, and they often have metabolic inflammation that is chronic and involves chronic myeloid cells. This inflammation is triggered by glycosphingolipid-loaded macrophages [8]. Given that the hypercytopenia associated with Gaucher's disease is similar to that which has been described in SARS-CoV-2, it is reasonable to assume that these patients will be at increased risk of developing a serious illness [9-11]. It is unknown whether or not receiving treatment for Gaucher disease has an impact on the progression of SARS-CoV-2 infection [4, 6, 10]. It is hypothesized that SARS-CoV-2 infection may bring about additional serious risks and co-morbidities in patients with Gaucher disease who have had their spleens removed in the past [12]. The purpose of this research was to investigate the effects that an infection with SARS-CoV-2 has on Gaucher patients.

**Materials and Methods**

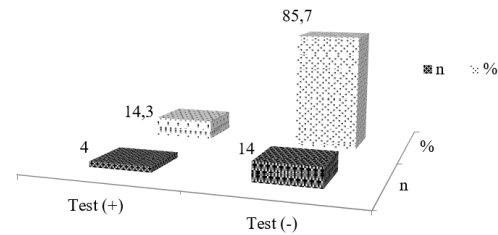
Our study was initiated with the approval of the Malatya Turgut Ozal University Clinical Research Ethics Committee (Date: 2022, Decision No: 18). Patients who had been monitored for a number of years with the diagnosis of Gaucher disease were invited to participate in the study between the months of August 2020 and September 2022. The results of patients who regularly came to the hospital for follow-up and treatment every two weeks and whose examinations were renewed every three months when necessary were retrieved retrospectively from the electronic records of the hospital as well as the files of the doctors who came after them. This was done in order to ensure accuracy. Patients diagnosed with Gaucher disease were questioned one-on-one to determine if they had come into contact with another person who had COVID-19 symptoms or another patient who had COVID-19. The patients were questioned and their answers were recorded regarding their GBA genotype, previous splenectomy history, whether or not they received treatment, and whether or not they had a SARS-CoV-2 test [13].

*Statistical analysis*

The characteristics of the participants as well as the symptoms and signs were measured in terms of mean and frequency before being subjected to Chi-square tests, t-tests, and logistic regression analyses. As a result of the non-specific nature of the COVID-19 symptoms, the thresholds for statistical evaluations were set at three or more. It was decided that each analysis would be exploratory, and the level of statistical significance in SAS was set at  $p < 0.05$  (SAS Institute Inc., Cary, NC).

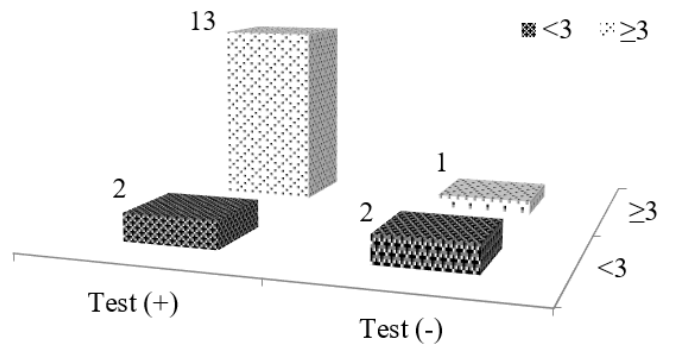
**Results**

Interviews were conducted with 24 patients who had previously been diagnosed with Gaucher's disease and were followed up on. There were 14 females and 10 males among these patients, and the mean age of the group was  $34.21 \pm 8.61$  years. The patients had all been diagnosed with Type 1 GD. There were no Ashkenazi Jews among our patients, despite the fact that Gaucher's disease is most prevalent in the Ashkenazi Jewish population. The majority of the cases were caused by a GBA



COVID-19 Symptom	Mean (sd)	p Value
Test positif	1	<0.001*
Test negatif	4	

**Figure 1.** Distribution of (+) and (-) states of test results (n; frequency, %; percent).



**Figure 2.** Distribution of 3 and higher than 3 and less than 3 symptom numbers in positive and negative.

mutation called p. N409S (N370S) (19). In 75% (18/24) of the cases, enzyme replacement therapy was being administered. Eight of our patients reported having contact with a COVID-positive or COVID-suspected individual. Of these eight cases, three (37.5% of the total) reported having at least one infection symptom, and two (25%) reported having more than three symptoms (Figure 2). There were 18 patients who were tested, and the results showed that 4 (22.2%) of those patients were positive for COVID-19; however, none of those patients had significant disease findings (Figure 1). 14 (or 77%) of the 18 patients who were tested returned negative results for the COVID-19. Patients typically presented with fever (54%), exhaustion (66%), cough (60%) and malaise (45%) as their most prominent symptoms. Positive results for COVID-19 were found in every patient who had reported three or more symptoms. (Table 1-3)

Eight of our patients (33%; 8/24) stated that they were in contact with someone with COVID-19 infection or suspected infection, and 3 of these cases (37.5%; 3/8) had at least 2 (25%) 3 cases. He stated that he had more than one symptom of infection, and the mean symptom frequency was 3.8. Of the 8 patients (62.5%) who were positive for COVID-19 and were in contact with the suspect, 5 (62.5%) had no symptoms and the tests were negative. The test was positive in 4 (22.2%) of the 18 patients who were tested, and the symptoms were significantly higher in

**Table 1.** Demographic data, comorbidities, GD treatments.

Demographic Data	n (%)
Gender (Female)	14 (58)
Gba Ns70s/Ns70s	24 (100)
<b>Comorbidity</b>	
Hypertension	3 (12.5)
Diabetes	1 (4.16)
Over-Weight	1 (4.16)
Lung Disease	1 (4.16)
Liver Disease	1 (4.16)
Kidney Disease	1 (4.16)
Cancer Story	0 (0)
Immune System Disease	0 (0)
Smoking History	5 (20.8)
Parkinson's History	1 (4.16)
Heart Disease	1 (4.16)
<b>Other</b>	
<b>Treatment</b>	
<b>Current Treatment</b>	
ERT	18 (75)
Total Treatment Time Mean (Sd) Years	6 (2.5-12)
Variable	Mean (Df)
Age, Mean (Sd)	35 (22-59)
BMI Mean (Sd)	25
Covid Symptom Mean (Sd)	
Comorbidity Mean (Sd)	

n; frequency, %; percent, df; degree of freedom ERT: Enzyme replacement therapy.

the positive patients than in the negative ones (3.8 vs 0.3,  $p < 0.001$ ). The test was positive in one patient who did not show any symptoms. Two of the cases had a history of splenectomy in their 20s, and one of these cases had extreme fatigue, weakness and cough.

Although one of the splenectomy cases had a history of contact with the case with COVID-19, the patient had neither symptoms nor a positive COVID-19 test. Only one (25%) of four patients over the age of 40 had symptoms and was COVID-19 negative. None of the Gaucher patients presented to the emergency unit, requiring admission to the intensive care unit or hospital. No patient with symptoms required specific treatment and symptoms could be controlled with antipyretics. No deaths were observed in our COVID-19 positive cases. We evaluated the findings that were effective in SARS-CoV-2 with logistic regression analysis. We found that comorbidities such as heart disease, diabetes and hypertension, age, gender and high BMI did not affect COVID-19 positivity in Gaucher patients. Among the symptoms, the biggest determinant of test positivity was the feeling of extreme fatigue.

Gba genotype and moderate or severe phenotype of symptoms were not related to test positivity. We found that ERT used in Gaucher disease was not associated with

being symptomatic and test positivity in SARS-CoV-2 (Table 1-3).

## Discussion

Our study is one of the rare studies on Gaucher patients in Turkey during the SARS-CoV-2 pandemic. Despite the fact that Gaucher disease has been reported as cases with clinical findings that resemble SARS-CoV-2 infection in Israel [14] and Europe [6, 15], the presence of infection has not been able to be verified despite the fact that such cases have been reported. In the cohort study that was carried out by Fierro et al. in New York on 181 cases of Gaucher disease, the researchers found that none of the cases had serious disease, despite the fact that the patients had mild symptoms and very few tests were positive. The patients in the study included 150 adults and 31 children [7]. In the study of Fierro et al., pulmonary and neurological involvements were observed quite frequently in pediatric patients with Type 3 Gaucher disease in pediatric patients with Type 3 Gaucher disease [6]. There was no evidence of such involvement in any of our patients because none of them had Type 3 Gaucher disease. All of our Gaucher disease patients had Type 1 GD.

Although approximately one in four of our patients stated that they were in contact with cases with COVID-19, nearly half of them had no symptoms and there were patients who reported symptoms without contact with

**Table 2.** Demographic findings, comorbidities and SARS-CoV tests in GD receiving treatment (n=18).

Demographic	Test positive n (%)	Test negative n (%)
Age mean (sd)	42.25	34.5
How many years has he been receiving treatment year (sd)	27	24
BMI	7.55	5.6
How many years has he been receiving treatment year (sd)	2 (50)	8(57.1)
Gender (female)	4 (100)	14 (100)
Gba N370S/NS70S		
Comorbidities	1	2
Hypertension	1	
Diabetes	1	
Over-Weight		1
Lung Disease		1
Liver Disease		1
Kidney Disease		
Cancer History		
Immune System Disease	2	3
Smoking History	1	
Parkinson's disease		1
Heart disease		
Other		
<b>Treatment</b>		
GD treatment used	4 (100)	14 (100)
ERT	4 (14.3)	14 (85.7)

BMI; body mass index, and Tx; treatment Percentages given in columns Percentage of patients tested in total Imiglucerase, velaglucerase used in ERT .

**Table 3.** Reported symptoms in our Gaucher patients number of patients n=24.

Symptoms	n (%)
Any COVID symptoms	13 (54)
3 or more COVID symptoms	2 (8.3)
Cough	2(8.3)
Fire	3 (12.5)
Night sweats and chills	2 (2.5)
Overstrain	4 (16.6)
Pain	3(12.5)
Stomach ache	1 (4.16)
Diarrhea	2 (8.3)
Taste Disorder	2 (8.3)
Olfactory Disorder	3 (12.5)
Bruising	-
Chest Pain	1 (4.16)
Difficulty Breathing	-
COVID-19 finger	-
Extreme Fatigue	3 (12.3)
Weakness	4 (16.6)
Other	-
SARS-CoV-2 test number (%)	
Throat Swab	
Test Positive	
3+symptoms	2 (50)
<3 symptoms	2 (0)
Test Negative	
3+ symptoms	1 (7.14)
<3 symptoms	13 (92.8)

n; frequency, %; percent.

COVID-19. In the cases that we looked at, it was discovered that the risk factors for severe SARS-CoV-2 infection were not connected in any way to the symptoms that the Gaucher patients were experiencing or to the positive test results.

In the course of our research, enzyme replacement therapy was administered to eighteen of the patients. In *in vitro* studies, glucosylceramide synthase inhibitors were shown to have protective effects; however, in our patients, the symptoms were less severe in those who were receiving treatment. (Table 1-3). In conclusion, our research has shown that the chronic inflammatory state that is characteristic of Gaucher disease is not associated with a greater risk of experiencing serious complications from SARS-CoV-2 infection. Through the transformation of natural killer cells into the THF phenotype and the promotion of B cell lympho proliferation in patients with Gaucher disease, it makes it easier to produce antibodies against SARS-CoV-2 infection. In the research carried out by Wajnberg et al., nine patients who had achieved seroconversion reported that moderate or high titer antibodies had been formed and that the immune response had been maintained in a robust manner [16]. These patients also stated that due to the limitations of the pandemic process, serum and/or plasma samples were taken regularly in the cases, but these measurements could not be studied. They stated that these antibodies shield patients suffering from

Gaucher disease from COVID-19 [6].

According to the findings of Zimran et al., in their group of 550 individuals from Israel and Australia, there was not a single instance of a life-threatening disease. They believe that glycosphingolipids accumulated in patients with GD when exposed to COVID-19 mainly support immune tolerance rather than inflammation, which means that they do not cause serious illness as was previously thought. However, in order to say anything definitive, decisions need to be made by an international consortium first. Zimran et al. stated that since glycosphingolipids can affect the immune system in opposite directions, they think that glycosphingolipids accumulated in patients with GD when exposed to COVI stated that preparations should be made for it [15]. No patient developed a serious illness; therefore, none of our patients required hospitalization; instead, they were treated as outpatients with supportive treatments.

We believe that those who follow and treat Gaucher patients can benefit from the experience of these patients by following the results of these studies. This is because there has been an increase in the number of SARS-CoV-2 cases reported around the world [17]. As a result of the fact that the majority of these studies were carried out during the pandemic, there were a lot of restrictions; in order to get more accurate results, we need studies that involve a large number of patients.

## Conclusion

In conclusion, our research revealed that patients with Gaucher disease did not have a severe infection with viral respiratory infection despite the presence of increased risk factors. We think that glycosphingolipids accumulated in patients with GD mainly promote immune tolerance rather than inflammation when exposed to viral respiratory infection. However, to say anything definitive can be judged by the results from multicenter studies and the rare diseases community. As glycosphingolipids may affect the immune system in opposite directions, we think that glycosphingolipids accumulated in patients with GD promote immune tolerance rather than inflammation. In patients with Gaucher disease, a metabolic inflammation that results in lysosomal dysfunction and B-cell lymphoproliferation provides a protective effect against infection with viral respiratory infection. It was determined that additional research on this topic should be carried out with a greater number of participants per study.

## Ethical approval

The study was initiated with the approval of the Malatya Turgut Ozal University Clinical Researches Ethics Committee (Date: 2022, Decision No: 18).

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