DOI: 10.37990/medr.1139421 Med Records 2023;5(2):231-6

MEDICAL RECORDS-International Medical Journal

Research Article

# COVID-19 Infection in Patients with Gaucher Disease

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**Abstract**

**Aim:** Coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome with a high mortality rate and has been labeled a global pandemic in March 2020. Gaucher Disease (GD) is one of the rare inherited lysosomal storage diseases (LSDs). We aimed to call attention to the frequency, susceptibility of COVID-19 infection, and the factors that prevent this infection in patients with GD as compared to other LSDs.

**Material and Methods:** The study was conducted retrospectively between September and December 2020. Participants were divided into two groups: GD group (19 patients) and the control group (19 patients, those with other LSDs). All patients were contacted by phone to collect data about their health status, and any possible contact with Covid-19 patients.

**Results:** Six of the GD patients (36.8%) had contacted a confirmed COVID-19 infected person but only three (15.8%) had developed a mild COVID-19 with fever and fatigue that did not require hospital admission. Four of the control group patients (21.1%) had experienced contact with a person with a confirmed COVID-19 infection. Three of the control group patients, that comprised of patients with various LSDs other than GD (15.8%) were positive on COVID-19 PCR tests and two of them had developed a mild COVID-19 infection. One of these (with Mucopolysaccharidosis type 1) had severe symptoms and required hospitalization.

**Conclusion:** There is no consensus on the management of rare diseases such as lysosomal storage diseases during the COVID-19 pandemic. Developing plans regarding the management of COVID-19 infections in LSDs will be useful when drawing up consensus guidelines.

**Keywords:** Gaucher disease, lysosomal storage disorders, COVID-19

## INTRODUCTION

Lysosomal storage disorders (LSDs) are metabolic disorders that are caused by the storage of various substrates in the lysosomes. LSDs are mostly inherited autosomal recessively and the prevalence is approximately 1 in 4000 live births (1). The relevant clinical features are associated with substrate storage in the organs and systems including the heart, kidneys, skin, upper respiratory tract, lungs, and intestines. Symptoms may appear anytime from the newborn period to late adulthood (2).

Gaucher Disease (GD) is a genetically inherited LSD that occur due to homozygous variations in the GBA1 gene that causes diminished function of the lysosomal glucocerebrosidase enzyme and thus, glucocerebrosides accumulate in macrophages of various tissues (2). The disease is categorised as the non-neuronopathic (GD type 1) and neuronopathic (GD type 2 and GD type 3) types. Some patients that have previously undergone splenectomy due to hypersplenism can develop pulmonary vascular complications (3,4).

Many treatment options that are useful on many of the systemic non-neurological manifestations of GD are available including substrate reduction therapy (SRT) and enzyme replacement therapy (ERT) (5,6).

Chronic inflammation, immune dysfunction, coagulopathy and fibrinolysis have recently all been shown to be the underlying pathogenic mechanism in GD (7). The presence of activated macrophages and pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 6 and 10 (IL6, IL10) and have been reported in patients with

CITATION
Urey BC, Kasapkara CS, Inci A, et al. Comparison of Platelet Parameters and Electrocardiogram Data in Patients with Generalized Anxiety Disorder with Healthy Control Group. Med Records. 2023;5(2):231-6. DOI:1037990/medr.1139421

**Received:** 05.09.2022 **Accepted:** 01.03.2023 **Published:** 23.03.2023
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GD (8). In addition, elevated serum angiotensin converting enzyme (ACE) is thought to be the result of production by Gaucher cells, reflect disease activity in GD (9).

Coronavirus disease 2019 (COVID-19) is a severe disease caused by the COVID-19 virus (10). People with chronic diseases are at higher risk of severe effects during this pandemic (11).

In this study, we aimed to analyze the frequency of COVID-19 infection, susceptibility to COVID-19 infection, and the preventive factors in patients with GD as compared to other LSDs.

## MATERIAL AND METHOD

Permission to conduct the study was obtained from the local ethics committee (Approval date: 16.09.2020, approval number: E1-20-1173). The study was compatible with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000. Written consent was obtained from all participants. The subjects were divided into two groups as those with GD (named as Gaucher group) and those with other LSds (named as control group). Data were collected from the hospital records. All patients were contacted by phone to collect data about their health conditions, and any possible contact with Covid-19 patients. Laboratory tests including enzyme activity measurement, molecular genetic analysis, and angiotensin converting enzyme level determination were conducted.

Lysosomal enzyme activities were evaluated in leukocytes extracted from whole blood samples. Molecular genetic analysis was performed on DNA isolated from EDTA blood samples. Angiotensin converting enzyme levels were analyzed with the turbidimetric method from a biochemistry blood sample.

Descriptive statistics were used to express the results as the median and range. The Kolmogorov-Smirnov test was used to test the distribution of the variables, and the Mann-Whitney U test for the analysis of quantitative independent data. The chi-square test was used for the analysis of qualitative independent data, while the Fisher test was used when the chi-square test conditions were not met. The SPSS 27.0 software was used for the analyses.

## RESULTS

The study was conducted retrospectively between September and December 2020. The Gaucher group consisted of 19 patients with GD (Table 1), with 8 males (42.1%) and 11 females (57.9%). Most of the patients in this group had type 1 GD (15/19, 78.9%) while 4 patients had type 3 GD (21.2%). The GBA analysis revealed that the most common genotype was detected as c.1226A>G (N370S) in type 1 GD and c.1448T>C (L444P) in type 3 GD. All patients were receiving ERT at the hospital but 6/19 (31%) patients reported that they had missed few doses at the beginning of the pandemic, without experiencing any bone-related or metabolic crisis.

**Table 1. The gaucher disease patients' general characteristics**

| Gaucher Group | | Min-Max | Median | Mean SD±(n%) |
|---|---|---|---|---|
| **Age** | | 2.0 - 38.0 | 22.0 | 20.6±11.1 |
| **Age at diagnosis** | | 1.0 - 30.0 | 7.0 | 8.4±7.9 |
| **ACE enzyme level** | | 25.0-82.6 | 35.0 | 44.7±21.5 |
| | | **N (%)** | | |
| **Gender** | Female | 11 (57.9%) | | |
| | Male | 8 (42.1%) | | |
| **Subtype of GD** | Type I | 15 (78.9%) | | |
| | Type III | 4 (21.1%) | | |
| **Genetic analysis** | L444P | 5 (26.3%) | | |
| | N370S | 14 (73.7%) | | |
| **Disruption of enzyme therapy?** | Yes | 13 (68.4%) | | |
| | No | 6 (31.6%) | | |
| **History of COVID-19 infection?** | No | 16 (84.2%) | | |
| | Yes | 3 (15.8%) | | |
| **Contact with COVID-19 infected person?** | No | 12 (63.2%) | | |
| | Yes | 7 (36.8%) | | |
| **Splenectomy status** | No | 16 (84.2%) | | |
| | Yes | 3 (15.8%) | | |

ACE: Angiotensin converting enzyme

Six of our patients with GD (36.8%) had contacted a confirmed COVID-19 infected person but only three (15.8%) were PCR-positive for COVID-19 with a nasal swab test and had developed mild symptoms with fever and fatigue. Two of these affected patients had undergone splenectomy. The median ACE level was 35 U/L and the mean 44.7±21.5 U/L (range 8-52). ACE levels of patients before the initiation of ERT were unavailable.

The control group included 19 patients consisting of 10 females (52.6%) and 9 males (47.4%) with a median age of 9 years and mean age of 14.7±17.1 years (Table 2). These patients had other LSDs such as Pompe disease, Metachromatic Leukodystrophy (MLD), Fabry disease, and Mucopolysaccharidosis (MPS). The diagnoses consisted of Fabry disease (4 patients), Pompe disease (3 patients), MLD (2 patients), Mucopolysaccharidosis (5 patients consisting of 1 patient with type 1, 2 patients with type

**Table 2. The control group's general characteristics**

| Control Group | | Min-Max | Median | Mean |
|---|---|---|---|---|
| **Age** | | 2.5-59.0 | 9.0 | 14.7±17.1 |
| | | **N (%)** | | |
| **Gender** | Female | | 10 (52.6%) | |
| | Male | | 9 (47.4%) | |
| **Subtype of LSD** | Fabry | | 4 (21.1%) | |
| | Pompe | | 4 (21.1%) | |
| | MLD | | 2 (10.5%) | |
| | Krabbe | | 1 (5.3%) | |
| | MPS Tip 1 | | 1 (5.3%) | |
| | MPS Tip 2 | | 2 (10.5%) | |
| | MPS Tip 3 | | 2 (10.5%) | |
| | Niemann-Pick Type B | | 1 (5.3%) | |
| | Niemann-Pick Type C | | 1 (5.3%) | |
| | Wolman | | 1 (5.3%) | |
| **Disruption of enzyme therapy or substrate reduction therapy** | Yes | | 8 (61.5%) | |
| | No | | 5 (38.5%) | |
| **History of COVID-19 infection?** | No | | 16 (78.9%) | |
| | Yes | | 3 (21.1%) | |
| **Contact with COVID-19 infected person?** | No | | 15 (78.9%) | |
| | Yes | | 4 (21.1%) | |

MLD: Metachromatic leukodystrophy, MPS: Mucopolysaccharidosis

**Table 3. The comparison of the characteristics of gaucher group and control groups**

| | | Control Group | | Gaucher group | | P |
|---|---|---|---|---|---|---|
| | | **Mean ± SD** | **Median** | **Mean ± SD** | **Median** | |
| **Age** | | 20.6±11 | 22 | 14.7±17.1 | 9.0 | 0.029m |
| | | **N (%)** | | **N (%)** | | |
| **Gender** | Female | 11 (57.9%) | | 10 (52.6%) | | 0.744X² |
| | Male | 8 (42.1%) | | 9 (47.4%) | | |
| **Disruption of enzyme therapy or substrate reduction therapy** | Yes | 13 (68.4%) | | 8 (61.5%) | | 0.734X² |
| | No | 6 (31.6%) | | 5 (38.5%) | | |
| **History of COVID-19 infection?** | No | 16 (84.2%) | | 16 (78.9%) | | 0.738X² |
| | Yes | 3 (15.8%) | | 3 (21.1%) | | |
| **Contact with COVID-19 infected person?** | No | 12 (63.2%) | | 15 (78.9%) | | 0.283X² |
| | Yes | 7 (36.8%) | | 4 (21.1%) | | |

m: Mann-Whitney u test / X² Chi-square test

2 and 2 patients with type 3), Krabbe disease (1 patient), Niemann-Pick disease type B (1 patient), Niemann-Pick disease type C (1 patient), and Wolman disease (1 patient). 12/19 of our patients in control group (68.4%) (with diagnoses of Fabry disease, MPS type1 and type 2, Pompe disease, and Wolman disease) were routinely receiving ERT while one patient with Niemann-Pick disease type C was receiving SRT. Eight patients in the control group had missed several doses during the pandemic.

Four patients in control group (21.1%) had experienced contact with a person with a confirmed COVID-19 infection. Three patients in control group (15.8%) were positive on COVID-19 PCR tests and two of them had developed a mild COVID-19 infection. One of these (with MPS type 1) had severe symptoms such as high fever, pneumonia, and ARDS. This patient later required intubation, followed by extubation after one week of hospitalization. She was discharged from the hospital after one month of treatment.

The age of the patients in the GD group was significantly higher than in the control group ($p<0.05$). Gender distribution and the rate of enzyme replacement therapy disruption in the Gaucher and control groups did not differ significantly ($p>0.05$). There was also no significant difference between the COVID-19 infection rate ($p>0.05$) or the contact history rate ($p>0.05$) in the Gaucher and control groups (Table- 3).

## DISCUSSION

Lysosomal storage disorders (LSDs) are characterized by the accumulation of storage materials in the lysosomes. leading to severe multisystemic effects (19). The treatment of many LSDs consist of ERT or other oral drugs (20).

GD is caused by variants in the GBA1 gene, that is located on 1q21, and inherited autosomal recessively. The mutation leads to disturbed activity of the lysosomal glucocerebrosidase, that is responsible for the hydrolyzation of glucosylceramide (GlcCer) into ceramide and glucose. Three subgroups have been defined for GD. Type 1, the most common form, does not cause neurological damage, on the contrary, types 2 and 3 lead to neurological dysfunction (21).

Sphingolipids are known to be involved in inflammation and apoptosis, and glucosylceramide has been suggested to have direct effects on macrophage function. Several markers of macrophage activation (chitotriosidase, CCL18, and angiotensin-converting enzyme) have been detected in the plasma of patients with GD (22).

COVID-19 is the coronavirus that has caused the current pandemic (23,24). Angiotensin-converting enzyme 2 is a homologue of angiotensin-converting enzyme (ACE), which is the functional receptor of COVID-19.

COVID-19 infection has been recognized to develop in three stages. In stage I, the virus particles bind to an ACE2 receptor and endolysosomal processing starts. Early symptoms that include fatigue, cough, and fever can develop in this stage (12,13). Most patients recover at this stage. Progression to the second stage with pulmonary disease (with or without hypoxemia) is seen in 15% of the patients and chest X-ray or CT scan will reveal diffuse pulmonary infiltrates or ground glass opacities (14). The third stage occurs in 5% of the patients and can cause systemic inflammation, multiorgan involvement, and acute respiratory distress syndrome (ARDS) (15,16).

ACE2 is the functional receptor of COVID-19 and plays an important role in the pathogenesis of COVID-19 as it enables viral entry into human cells (17). ACE2 is a zinc-metallopeptidase that acts as an antagonist of ACE. ACE converts angiotensin I to angiotensin II which is a vasoconstrictor. ACE also breaks down bradykinin, a vasodilator. The main role of ACE2 is to convert Ang II to Ang I, thus counteracting the effects of Ang II as a pressor, proliferative agent, and pro-fibrotic agent (18).

The similarities between GD and COVID-19 infection are striking. Both diseases show lysosomal involvement, destruction, activated hypercytokinemia pathway, and a proinflammatory response.

The study population included 19 patients with Gaucher disease consisting of 8 males (42%) and 11 females (58%) with a median age of 19 years (range 2-38). Fifteen of our patients with Gaucher disease (78.9%) had type 1 disease while the remaining four cases were type 3. The GBA analysis revealed that the most common genotype was detected as c.1226A>G (N370S) in type 1 GD and c.1448T>C (L444P) in type 3 GD.

All subjects with GD were receiving ERT at the hospital. Six of the 19 patients (31%) reported that they missed few doses at the beginning of the pandemic but they had not experienced any bone-related or metabolic crisis. A study from Spain has reported that 25% of Gaucher patients that received ERT missed several doses during the pandemic, and again did not suffer any bone-related complaints or acute bone pain. However, the worldwide enzyme production has caused bone crisis, bone pain, anemia, and thrombocytopenia some patients around the world (24).

The Spanish Gaucher Disease Foundation has surveyed 113 GD patients. Six of the patients reported to contact with a confirmed COVID-19 infected person. Two previously splenectomized GD patients developed COVID-19 infection. One developed severe symptoms and died due to multiorgan failure while the second had mild symptoms and did not require hospitalization (25). Zimran et al. have studied 550 adult GD patients and found only one patient with confirmed COVID-19 infection, in this case with a mild clinical course (2).

Several blood biomarkers such as angiotensin-1-converting enzyme (ACE), chitotriosidase, and acid phosphatase have been identified for GD (24). The angiotensin converting enzyme levels were high in only 2 of our 19 GD patients (10%). These generally lower ACE levels in our group are thought to be related by receiving regular enzyme replacement therapy.

Although Ballout et. al have proposed that the inherent cellular and biochemical abnormalities of LSDs, especially Niemann-Pick disease type C (NPC) create possibly "unfavorable" environments for COVID-19 infectivity in the corresponding host cells (25), patients with LSDs are at high risk of severe symptoms because of multisystem involvement. The tests of 3 patients in the control group were positive for COVID-19, and two of them developed mild COVID-19 infection. One case with the diagnosis of MPS type 1 experienced severe symptoms such as high fever, pneumonia, and ARDS requiring intubation. The other two patients were mother and son who had both mild infection. None of the remaining patients had symptoms of Covid-19 and therefore, PCR tests were not performed. Eight patients (61,5%) in the control group had missed several doses during the pandemic. A study of 102 patients in Italy interviewed during the pandemic found that 77.5% were receiving ERT at the hospital and 22.5% were on home therapy, of which 100% continued to take their medication except one, while 49% of the patients receiving ERT at the health care facilitites experienced treatment interruptions although no one was infected, which may be explained by the attention of these patients to hygiene and infection prevention measures (26). The control group of our study consisted of patients with LSDs other than GD. Although this situation might be considered as a limitation, the main principle of our study was to evaluate the effects of COVID-19 infection on GD with respect to other LSDs. Our study has clearly showed that GD patients may have a better prognosis of SARS-CoV-2, when compared to other LSDs.

## CONCLUSION

In conclusion, there was no sign of severe infection in our Gaucher Disease patients, probably because they received their ERT treatment regularly and paid more attention to the hygiene rules due to their underlying diseases with compared to the normal population.The ACE levels were not very high in our patients with GD because they had been receiving ERT treatment regularly for more than a year and none of our patients had been recently diagnosed. There is no consensus management of rare diseases such as lysosomal storage diseases during the COVID-19 pandemic. Developing plans regarding complications of lysosomal storage diseases as related to COVID-19 infections will be useful when drawing up consensus guidelines.

***Financial disclosures:*** *The authors declared that this study hasn't received no financial support.*

***Conflict of Interest:*** *The authors declare that they have no competing interest.*

***Ethical approval:*** *Permission to conduct the study was obtained from the local ethics committee Ankara city hospital (Approval date: 16.09.2020, approval number: E1-20-1173).*

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