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COVID-19 and Vaccination Status in Lysosomal Storage Diseases: A Single-Center Experience

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What is already known on this topic?

- *Lysosomal storage diseases are chronic progressive multisystem diseases with substance accumulation. Coronavirus disease (COVID-19) causes significant morbidity and mortality in individuals with chronic disease. A rapidly initiated vaccination program is the most crucial factor in the mild recovery of the illness.*

What this study adds on this topic?

- *The disease course of COVID-19 in lysosomal storage diseases remains uncertain. This study shows lysosomal storage disease patients do not have an increased risk of COVID-19 compared to the population despite the chronic inflammatory disease. Increasing the vaccination rate in lysosomal storage disease patients will be protective against COVID-19.*

ABSTRACT

Objective: Coronavirus disease 2019 (COVID-19) causes significant morbidity and mortality in individuals with chronic disease. There is not enough information about the course of coronavirus disease in lysosomal storage diseases. This study aimed to evaluate coronavirus disease vaccination status and the impact of coronavirus disease on lysosomal storage disease.

Materials and Methods: The study included 87 lysosomal storage disease patients. The patients' diagnoses were Gaucher, mucopolysaccharidosis I, II, IVA, VI, VII, Fabry, and Pompe. A questionnaire assessing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure, coronavirus disease symptoms, and vaccine status was administered in person or by phone calls.

Results: The number of coronavirus disease positive patients was 8 (9.1%). Only 2 patients were treated in the intensive care unit. Other coronavirus disease patients had mild symptoms and stayed in-home quarantine. Patients over 12 years of age could receive a COVID-19 vaccine. 63.5% of those aged ≥12 years were vaccinated.

Conclusion: Lysosomal storage disease patients did not have an increased risk of COVID-19 compared to the healthy population, despite the chronic inflammatory disease. Vaccination of lysosomal storage disease patients will be protective against severe coronavirus disease.

Keywords: COVID-19, fabry, Gaucher, inherited metabolic diseases, lysosomal storage diseases, SARS-CoV-2

INTRODUCTION

Lysosomal storage diseases (LSDs) are chronic metabolic diseases characterized by the accumulation of toxic substances due to enzyme deficiencies. The accumulation of these substances causes progressive multisystemic disease.[1] Disease-specific enzyme replacement therapy (ERT) is used in some LSDs. Despite treatment, comorbidities can occur with the disease. Lysosomal storage diseases treated with ERT are mucopolysaccharidosis (MPS) I, MPS II, MPS IVA, MPS VI, MPS VII, Pompe, Fabry, and Gaucher disease.[2]

Coronavirus disease (COVID-19), which started with viral pneumonia cases of unknown cause in China, in December 2019, spread to the whole world in March 2020, causing a pandemic. The disease shows a heterogeneous course from an asymptomatic case to an acute respiratory distress syndrome (ARDS) clinic requiring follow-up in the intensive care unit.[3] A close relationship exists between chronic diseases such as diabetes, hypertension, cardiovascular diseases, and chronic obstructive pulmonary disease (COPD) and COVID-19.[4] However, there is not enough information about LSD, which is chronic, and its risk of COVID-19. In the

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literature, LSD patients have been reported with COVID-19 mildly.[5-9] The vaccine has been developed quickly to prevent COVID-19.[10,11] In our country, all individuals over 12 years are allowed to be vaccinated, currently.[12]

In this study, we aimed to determine the COVID-19 vaccination status and the impact of COVID-19 in patients with MPS I, MPS II, MPS IVA, MPS VI, MPS VII, Pompe, Fabry, and Gaucher diseases.

MATERIALS AND METHODS

Patients followed up with MPS I, MPS II, MPS IVA, MPS VI, MPS VII, Gaucher, Pompe, and Fabry disease in a single center's department of metabolism were included in the study. All patients were diagnosed by enzymatic and genetic analysis. The demographic data, including patient age and gender, general clinical characteristics, comorbidities (high blood pressure, diabetes, overweight, lung disease, liver disease, kidney disease, history of smoking), and treatment history, were retrieved from their medical records retrospectively.

A questionnaire assessing contact with a person who tested positive for COVID-19, COVID-19 positivity, symptoms of COVID-19, and vaccine status (number of doses and intervals, vaccine selection) was administered in person or by phone calls. A positive nasal swab polymerase chain reaction (PCR) test determined COVID-19 positivity. The data of patients who tested positive for SARS-CoV-2 infection were analyzed for the signs, course, and severity of COVID-19 between April 2020 and December 2021. Severe cases were defined based on ARDS or admission to ICU.[13] The participants' COVID-19 data were confirmed by health registries beyond the telephone appointments. Routine laboratory findings of patients with COVID-19 were evaluated if the patient had a laboratory analysis within 1 month before COVID-19 and 1 month after COVID-19.

The study was carried out following the Declaration of Helsinki. The patients or their relatives obtained an informed consent form. The study was approved (approval number: 22-2T/17) by the ethics committee of Ege University.

Statistical Analysis

Statistical Package for Social Sciences version 22.0 (IBM Corp.; Armonk, NY, USA) was used for the statistical analysis. Qualitative data were presented as counts and percentages. Quantitative data were given as mean ± standard deviation for normally distributed data or otherwise median and range. The Kolmogorov–Smirnov test was performed to assess the normality of the numeric variables.

RESULTS

Baseline Characteristics

The study included 33 Gaucher, 16 MPS IVA, 11 MPS VI, 10 MPS II, 9 Fabry, 4 Pompe, 3 MPS I, and 1 MPS VII patient. The median age of the patients was 15.7 years (min 4 months, max 70 years), and there were 41 males and 46 females. A total of 36.7% of the LSD patients had comorbidity. The most common comorbidities were heart disease (12.6%), lung disease (8%), and smoking history (8%). A total of 19 (21.3%) LSD patients had a history of contact with COVID-19 patients. For 2 patients with a history of contact, the PCR test was positive for SARS-CoV-2. Three patients had a history of contact and had symptoms, but PCR was negative. The test was not performed in 3 patients despite the history of contact and symptoms (sore throat, headache, new loss of smell or taste). Eleven patients had a history of contact but did not have symptoms; a PCR test was not performed. In 8 (9.1%) of 87 patients, COVID-19 was confirmed by PCR test. Six of the patients with COVID-19 had no history of contact. The demographic data, comorbidity status, and contact history of COVID-19 are presented in Table 1.

Vaccination Data

As shown in Table 2, 21 (37%) of 57 patients over 12 years of age were not vaccinated. The vaccine choice was 32% BioNTech, 23% CoronaVac, and 9% both. Regarding the dose preference in patients with the COVID-19 vaccine, 11% received 1 dose, 64% received 2 doses, and 25% received 3 doses. Only 51.6% of the patients were vaccinated with at least 2 doses of the COVID-19 vaccine.

Patients with Coronavirus Disease

COVID-19 occurred in 8 patients (9.1%). Two of eight patients had severe COVID-19. A 14.8-year-old female patient with MPS I was not vaccinated. She presented with a fever and cough. Coronavirus disease pneumonia was detected. Leukopenia (2260 µL, normal: 4500-13 000) and thrombocytopenia (97 000 µL, normal: 150 000-450 000) were found on admission to the hospital. On the third day of infection, white blood cell and thrombocyte values returned to normal. She was intubated in the intensive care unit for respiratory distress for 17 days. She was treated with antibiotics, favipiravir, steroids, and anticoagulants and then she recovered. A 21-year-old male patient with MPS VI presented with shortness of breath. He tested positive for COVID-19. He received the first dose of the BioNTech vaccine 7 days before COVID-19. He was hospitalized and treated in the intensive care unit for 19 days. He had no cytopenia before or after COVID-19. He was intubated and treated with anticoagulant, steroid, favipiravir, tenofovir, and intravenous immunoglobulin and then he recovered.

Our other 6 patients did not hospitalize or did not require COVID-19-specific treatments. The symptoms recovered about 5-10 days. Five patients with COVID-19 had complete data to be evaluated for laboratory testing. Cytopenia was noted in 2 patients. One of them, the MPS I patient with severe COVID-19 is mentioned above. The other was a Gaucher female patient with mild COVID-19 in whom leukopenia was detected on the 14th day after COVID-19. There was a 2-week ERT disruption due to her quarantine. Leukopenia returned to normal within 1 month. There were no significant differences in the laboratory evaluations of the other 4 patients. The patients who had COVID-19 are detailed in Table 3.

In one of our patients with MPS II, sudden death occurred during the quarantine process at home while the parents were infected with COVID-19. Polymerase chain reaction could not be performed on this patient, but we thought his death might be related to COVID-19.

DISCUSSION

This study on LSD patients investigated the relationship between LSDs and COVID-19. It is known that chronic diseases and comorbidity increase the severity of COVID-19. A rapidly

Table 1. Patient Characteristics

	MPS I (n = 3)	MPS II (n = 10)	MPS IVA (n = 16)	MPS VI (n = 11)	MPS VII (n = 1)	Gaucher (n = 33)	Fabry (n = 9)	Pompe (n = 4)	Total (n = 87)
Age, mean (SD), years	12.8 (5.3)	9.2 (4.4)	13.3 (8.7)	12.6 (6.9)	32	29.8 (17.2)	33.7 (15.5)	3.8 (3.7)	20.9 (15.9)
Gender n (%)									
Male	0	10	7	4	1	11	5	3	41 (47.1%)
Female	3	0	9	7	0	22	4	1	46 (52.8%)
Comorbidities, n (%)									
High blood pressure	-	-	-	1 (9%)	–	1 (3%)	4 (44.4%)	-	6 (6.8%)
Diabetes	-	-	–	1 (9%)	-	2 (6%)	1 (11.1%)	-	4 (4.5%)
Overweight	-	-	-	2 (18.1%)	-	0	–	-	2 (2.2%)
Lung disease	-	1 (10%)	1 (6.2%)	2 (18.1%)	-	2 (6%)	–	1 (25%)	7 (8%)
Liver disease	–	–	-	–	–	–	0	-	0
Kidney disease	-	-	-	-	-	-	-	-	-
History of smoking	-	-	-	-	-	6 (18.1 %)	1 (11.1%)	-	7 (8%)
Heart disease	-	-	2 (12.5%)	3 (27.2%)	-	4 (12.1%)	2 (22.2%)	-	11 (12.6%)
Other	-	1 (10%)	-	-	-	2 (6%)	-	1	4 (4.5%)
SARS-CoV-2 infection, n (%)	2	0	1	1	0	3	1	0	8 (9.1%)
History of contact, n (%)									
Yes	1	1	3	4	-	9	2	-	19 (21.8%)
No	3	9	13	7	1	24	7	4	68 (78.1%)

COVID-19, coronavirus disease; MPS, mucopolysaccharidosis; SD, standard deviation.

initiated vaccination program is the most crucial factor in the mild recovery of the illness.[10,14] Although the overall vaccination rate in Turkey is 89.9%,[15] the vaccination rate in LSD patients was recorded as 63% in our study. Our findings show that despite the high comorbidity and low vaccination rate, the number of patients (2.2%) with severe COVID-19 was few.

According to Pieroni et al.[16] there is potential resistance to SARS-CoV-2 infection in LSD patients. After the SARS-CoV-2 virus enters the cell, viral replication spreads in the endolysosome at an acidic pH. In LSD, glycosphingolipid storage disrupts various lysosomal functions, such as endosomal maturation and autophagy, thus leading to an "unfavorable" host for the virus.[16] In a study of LSD patients, however, almost half of the patients had abnormalities in autoimmunity or immunodeficiency parameters; just a few had COVID-19.[8]

It has been hypothesized that, stated in transcriptome analysis, MPS patients may be less susceptible to SARS-CoV-2.[17] Additionally, narrow respiratory tracts and thick mucus in MPS patients are risk factors for COVID-19.[18] In this study, MPS patients experienced the most severe COVID-19; 2 MPS patients were treated in the intensive care unit. One of the patients died with the suspicion of COVID-19 disease.

Laney et al[19] addressed common pathogenesis and target organs between Fabry disease and COVID-19. Both groups can cause stroke, heart, and lung involvement, severe kidney disease, micro/macrothrombus due to endothelial dysfunction, systemic inflammation, and gastrointestinal and skin disease.[20] Especially heart and kidney transplantation, male gender, and over 40 are risk factors for severe COVID-19 disease. Complicated Fabry disease could cause a more severe

Table 2. Patients Over 12 Years and COVID-19 Vaccines

	MPS I (n = 2)	MPS II (n = 2)	MPS IVA (n = 8)	MPS VI (n = 6)	MPS VII (n = 1)	Gaucher (n = 29)	Fabry (n = 9)	Pompe (n = 0)	Total (n = 57)
Age, mean (SD), years	15.8 (1.4)	16.6 (2.6)	19.2(8.6)	17.6 (4.1)	32	32.9 (16.1)	33.7 (15.5)	-	28.3 (15)
Gender									
Male	0	2	3	3	1	9	5	-	23
Female	2	0	5	3	0	20	4	-	34
COVID-19 vaccination									
Yes	1	0	4	4	1	19	7	-	36
No	1	2	4	2	0	10	2	-	21
BioNTech	1	-	3	2	1	12	4	-	23
CoronaVac	-	-	1	2	-	11	4	-	18
Dosage									
1 dose	-	-	-	1	-	2	1	-	4
2 doses	1	-	4	2	1	12	3	-	23
3 doses	-	-	-	1	-	5	3	-	9

COVID-19, coronavirus disease; MPS, mucopolysaccharidosis; SD, standard deviation.

Table 3. Clinical Characteristics and Outcomes of Patients with COVID-19

	Patient 1	**Patient 2**	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 7**	**Patient 8**	**Patient 9**
Disease	**MPS I**	**MPS I**	**MPS IVA**	**MPS VI**	**Gaucher**	**Gaucher**	**Gaucher**	**Fabry**
Sex	Female	Female	Male	Male	Male	Female	Male	Male
Age (years)	16.9	14.8	10.2	21	43	67	70	36
Age at diagnosis (years)	2.8	3	7	4	6	63	65	24
Total years of ERT	14	11	2.8	15	11	1	4	12
ERT disruption time during COVID-19 pandemic	1 month	None	1 year	none	1 month	1 month	none	1 month
Vaccination status during COVID-19	2 BioNTech	None	None	1 BioNTech (7 days ago)	2 CoronaVac	2 CoronaVac, 1 BioNTech	2 BioNTech	None
Comorbidities	None	None	Heart disease	Hypertension Heart disease	Heart disease Lung disease	Diabetes	Diabetes	Hypertension Heart disease
COVID-x19 symptoms	Sore throat	Cough Fever	Cough	Dyspnea Cough	Sore throat	None	Fever	Weakness
History of contact	None	Contacted to symptomatic case	None	None	None	Contacted to symptomatic case	None	None
PCR for COVID-19	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
COVID-19 management	No treatment	Antibacterial Antiviral Anticoagulant Steroid Oxygen Intubation ICU	No treatment	Antibacterial Antiviral Anticoagulant Steroid Oxygen Intubation ICU	No treatment	No treatment	No treatment	No treatment

COVID-19, coronavirus disease; ERT, enzyme replacement therapy; ICU, intensive care unit; MPS, mucopolysaccharidosis; PCR, polymerase chain reaction.

COVID-19 clinic. However, in the experiences of the Fabry patients with COVID-19, severe illness and death were reported in only 2 individuals with comorbidities.[16,19,21,22] Karaca et al[7] reported that 5 out of 25 Fabry patients who had COVID-19 were hospitalized with major organ involvement, and 1 of them died. Our Fabry patient with COVID-19 had a mild disease in this study. Our patient with Fabry had hypertension and soft valvular involvement as comorbidities; he was under 40 and was not vaccinated.

Chronic inflammation, immune dysregulation, and increased activation in the fibrinolytic system seen in Gaucher patients are common findings that may also occur in the COVID-19 cytokine storm.[23] Many Gaucher patients have concerned about this situation.[24] However, severe COVID-19 with Gaucher disease has been reported rarely in the literature.[25-27] Hamiel et al[28] evaluated 1417 Gaucher cases from 10 countries. Eighty-two patients were infected with COVID-19; of the patients who had the infection, 83% survived mild, 11% were asymptomatic, and 2% as critical illnesses. Andrade-Campos et al[29] reported the only Gaucher case with COVID-19-related death, a 79-year-old patient with splenectomy and comorbidities. In another report, a pediatric case of Gaucher had a COVID-19 with a cavitary lung lesion.[30]

In a study evaluating 181 Gaucher patients, 45 had a history of contact with COVID-19, and only 38% of these patients developed COVID-19 symptoms. Similarly, symptoms developed in 42% of our contact patients in our study.[26] In a case from Turkey, in a Gaucher patient who had an asymptomatic COVID-19, there was an interruption in enzyme replacement treatment during the 2-month quarantine period. At the end of 2 months, cytopenia and increased chitotriosidase levels were observed.[31] In our study, leukopenia occurred after COVID-19 in 1 of our Gaucher patients. The leukopenia seen in our patient was thought to be secondary to infection rather than ERT interruption.

It is recommended that LSD patients should be vaccinated against COVID-19.[28,32] Nevertheless, COVID-19 vaccine resistance could be seen in some populations.[33] Previous studies reported that vaccination rates in inherited metabolic diseases were lower than in the healthy population.[34,35] Our study found that the vaccination rate in LSD patients was lower than in the population. At the same time, it was observed that COVID-19 was milder in LSD patients who had been vaccinated. Similarly, in our study, 1 patient with severe COVID-19 disease was not vaccinated, and the other was vaccinated before 7 days of COVID-19. Identifying the unmet needs and difficulties of patients with LSD is essential,[36,37] thereby overcoming patients' reservations about vaccination and encouraging them to vaccinate. This article has underlined the importance of informing and reassuring patients to increase vaccination rates.

CONCLUSION

The findings of this study support the idea that LSD patients do not have an increased risk of COVID-19 compared to the population, despite the chronic inflammatory state. However, it should be kept in mind that severe COVID-19 may develop in MPS patients due to a narrow airway and thick mucus formation. Increasing vaccination rates for LSD patients will be protective against severe COVID-19. New steps are needed to raise awareness and reassure patients. Establishing a national digital health platform about vaccines for LSD patients may be a good option for information.

Ethics Committee Approval: The study was approved by Ege University Medical Faculty Ethical Committee.

Informed Consent: Informed consent was obtained from the patients and their parents in this study.

Peer-review: Externally peer-reviewed.

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