



Impact of the COVID-19 Pandemic on Inherited Metabolic Diseases: Evaluation of Enzyme Replacement Treatment Adherence with Telemedicine

© Merve Yoldaş Çelik, © Ebru Canda, © Havva Yazıcı, © Fehime Erdem, © Sema Kalkan Uçar,
© Mahmut Çoker

Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Metabolism and Nutrition, İzmir, Turkey

ABSTRACT

Aim: During the coronavirus disease-2019 (COVID-19) pandemic, visiting the hospital and getting regular infusions can be difficult for patients with chronic illnesses. Telemedicine may offer a good option for the management of chronic diseases such as lysosomal storage diseases (LSD).

Materials and Methods: LSD patients at the Unit of Metabolic Diseases of Ege University were contacted by phone between April, 2020 and March, 2021 during the COVID-19 pandemic. Telemedicine appointments were performed at intervals every month or three months, depending on the patients' compliance with their treatment.

Results: Ninety-two LSD patients [Mucopolysaccharidosis (MPS) I, MPS II, MPS IVA, MPS VI, MPS VII, Gaucher, Fabry, and Pompe] were included in this study. The total skipped treatment rate within one year was 17.1%. Most of the months of interruption were consonant with the time of social isolation. The treatment interruption in patients under 18 years was lower than in patients over 18 years. A positive correlation was detected between the age of patients and the interruption of treatment.

Conclusion: The curfew periods might be one of the causes of missed treatment sessions. Telemedicine is a good method to improve the continuity of treatment. This study showed that the number of interrupted enzyme replacement treatments could be decreased via ongoing telemedicine appointments.

Keywords: Inherited metabolic diseases, Gaucher, Fabry, COVID-19, enzyme replacement treatment, telemedicine

Introduction

Coronavirus disease-2019 (COVID-19), caused by the severe acute respiratory syndrome-coronavirus-2 virus, was declared a global epidemic by the World Health Organization in March, 2021. The high morbidity and mortality rates of the COVID-19 infection are known (1). The Turkish Government

implemented intermittent lockdowns to limit the spread of COVID-19 starting in March, 2020 (2). During the COVID-19 pandemic, going to the hospital can be difficult for patients with chronic illnesses (3). To minimize disruption in health services, in some countries, a telemedicine application was started for chronic disease patients who could not come to health institutions due to the pandemic (4).

Address for Correspondence

Merve Yoldaş Çelik, Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Metabolism and Nutrition, İzmir, Turkey
E-mail: drmerveyoldas@yahoo.com ORCID: orcid.org/0000-0003-0015-9807

Received: 09.06.2022 Accepted: 19.07.2022

©Copyright 2022 by Ege University Faculty of Medicine, Department of Pediatrics and Ege Children's Foundation
The Journal of Pediatric Research, published by Galenos Publishing House.

Lysosomal storage diseases (LSD) have multi-organ involvement due to the accumulation of toxic substances in the lysosome. This condition can produce morbidity and mortality. Intravenous enzyme replacement therapy (ERT) is given to prevent the accumulation in some types of LSD. It should be applied regularly to get the maximum benefit from the treatment (5).

During the COVID-19 pandemic, many patients did not visit the hospital for fear of infection (3,6,7). Therefore, compliance in getting regular ERT infusions may be insufficient (8). Increasing the patient's motivation for compliance with the treatment by communicating via the telemedicine method may be a good option for the treatment management of these patients (9,10). In this study, we aimed to evaluate the compliance of LSD patients to treatment using the telemedicine method.

Materials and Methods

LSD patients who were followed up in the Ege University Faculty of Medicine, Department of Pediatric Metabolism and Nutrition, received ERT. Adherence to ERT was evaluated via telemedicine interviews between April, 2020 and March, 2021. The telemedicine appointments were performed by means of telephone calls to the patients. Telemedicine was performed at certain intervals according to the rate of treatment adherence. We performed a telemedicine appointment every month if the patient did not follow their treatment schedule properly, or when the physician deemed necessary. In those patients who were receiving regular ERT, telemedicine was performed at three-month intervals. Patients were advised not to interrupt their treatment during every telemedicine interview.

During telemedicine appointments, patients were questioned as to whether they had interrupted their treatment. Patients who did not comply with the therapy schedule were advised to follow the treatment program regularly. No other recommendations were made to the patients regarding their medical conditions.

All procedures followed were to the ethical standards of the Local Ethics Committee of Ege University (21-11.1T/43), and the Helsinki Declaration (2013). All patients or their parents included in this study gave informed consent to take part in this study.

The interruption of treatment percentages was calculated according to the number of infusions. The mean, standard deviation, median, minimum, maximum, frequency, and ratio values were calculated with the percentages of missing treatment and these were used in the descriptive statistics.

The minimum percentage (0%) was defined as patients who had missed all their infusions. Patients who had completed all their treatments were defined as maximum percentage (100%).

Statistical Analysis

The distribution of variables was evaluated with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used in the analysis of independent quantitative data. The Wilcoxon test was used to study dependent quantitative data. The Statistical Package for Social Sciences version 27.0 was used in the statistical analysis.

Results

Ninety-two LSD patients were enrolled in this study. The patients' details are shown in Figure 1. The mean age of the patients was 22.5 ± 16.6 years (min: 1.6, max: 70.0, median: 17.2). Forty-seven (51.1%) of the patients were female and 45 (48.9%) were male. ERT was given to MPS I, MPS II, MPS IVA, MPS VI, and Pompe patients once a week and MPS VII, Gaucher, and Fabry patients every two weeks. In one year, 317 telemedicine interviews were performed (Table I).

Our study evaluated the percentage of ERT disruptions at quarterly intervals. The total skipped treatment rate within one year was 17.1%. The most frequent interruptions in treatments occurred in April-May-June, 2020 and October-November-December, 2020 with rates of 23.6% and 19.7%, respectively (Table I). The Turkish Government imposed social isolation in some periods in order to prevent any unfavorable effects of the pandemic. The periods of the most frequent treatment skipping months were consonant with these times of social isolation. When treatment compliance was evaluated according to gender, there was no significant difference between females and

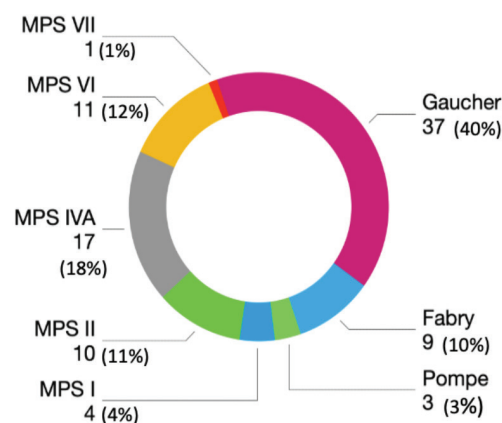


Figure 1. Distribution of the diseases

males with rates of 15.1% and 19.1%, respectively ($p=0.814$) (Table II).

Compliance with treatment was compared according to the age groups of under 18 years and over 18 years. The interruption of treatment in patients under 18 years was lower than patients over 18 years, with rates of 10.1% and 25.3%, respectively. A positive correlation was detected between the age of patients and the interruption periods of treatment ($p=0.040$) (Table II).

When the impact of disease groups was evaluated, the most frequent disruption of treatment was seen in the Gaucher group (22.1%). The second highest disruption of treatment rate was 18.8% in MPSIVA patients and the third highest rate was 17.4% in MPS VI patients. The high skipping rate of MPSIVA may be due to the three patients who did not receive any treatment for one year (Figure 2).

Due to the small number of individuals in the Fabry and Pompe groups, comparisons regarding missed treatment rates were made between MPS and Gaucher. There was no

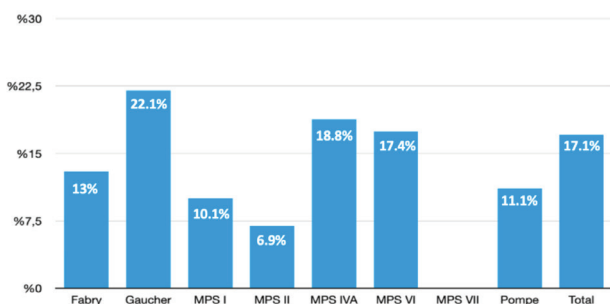


Figure 2. Treatment interruption percentages by patient groups

	Number of telemedicine visits (n)	Min.-Max.	Mean±SD
April-May-June 2020 Skipped treatment %	77	0.0-100.0	23.6±37.1
July-August-September 2020 Skipped treatment %	79	0.0-100.0	14.2±32.2
October-November-December 2020 Skipped treatment %	78	0.0-100.0	19.7±33.7
January-February-March 2021 Skipped treatment %	83	0.0-100.0	15.4±29.6
Total Skipped treatment %	317	0.0-100.0	17.1±26.3

	Female (n=47) Mean±SD	Male (n=45) Mean±SD	p-value
April-May-June 2020 Skipped treatment %	24.8±35.8	22.4±38.7	$p>0.05^m$
July-August-September 2020 Skipped treatment %	10.8±26.9	17.6±36.7	$p>0.05^m$
October-November-December 2020 Skipped treatment %	17.6±30.3	21.9±37.0	$p>0.05^m$
January-February-March 2021 Skipped treatment %	12.6±24.3	18.4±34.1	$p>0.05^m$
Total Skipped treatment %	15.1±20.5	19.1±31.3	$p>0.05^m$
	Age <18 (n=48) Mean±SD	Age >18 (n=44) Mean±SD	
April-May-June 2020 Skipped treatment %	16.9±31.9	31.6±41.4	$p>0.05^m$
July-August-September 2020 Skipped treatment %	6.0±21.0	23.1±39.4	$p=0.017^m$
October-November-December 2020 Skipped treatment %	10.3±23.5	30.0±39.9	$p=0.013^m$
January-February-March 2021 Skipped treatment %	9.2±21.1	22.8±36.0	$p=0.048^m$
Total Skipped treatment %	10.1±15.9	25.3±33.1	$p=0.040^m$
	MPS (n=43) Mean±SD	Gaucher (n=37) Mean±SD	
April-May-June 2020 Skipped treatment %	22.8±35.8	26.5±40.6	$p>0.05^m$
July-August-September 2020 Skipped treatment %	8.5±23.2	22.0±40.4	$p>0.05^m$
October-November-December 2020 Skipped treatment %	14.1±25.9	29.6±40.8	$p>0.05^m$
January-February-March 2021 Skipped treatment %	13.8±26.8	18.6±33.5	$p>0.05^m$
Total Skipped treatment %	14.4±20.3	22.1±31.7	$p>0.05^m$

^mMann-Whitney U test

significant difference in adherence to treatment between the MPS and Gaucher patients ($p=0.813$) (Table II).

Discussion

The COVID-19 infection was declared a pandemic in March, 2020 and it affected the whole world (1). Going to the hospital became challenging for patients with chronic illnesses during the pandemic. It has been reported that individuals with chronic diseases are more anxious and afraid of going to the hospital in a pandemic period (6). LSD are chronic diseases which result in the accumulation of toxic substances in the organs due to enzyme deficiency. Intravenous ERT is used to prevent this accumulation. Due to a fear of visiting hospitals during the pandemic, ERT was interrupted (11,12). Telemedicine is a good option for the ongoing management of chronic diseases and evaluating the patient's adherence to treatment and it has been widely used during the COVID-19 pandemic (4,13). However, increasing adherence to therapy with telemedicine may not always be successful. In our study, we evaluated the compliance to treatment of LSD patients using the telemedicine method over one year. To the best of our knowledge, this is the first long-term study in the literature to evaluate LSD patients' treatment compliance with telemedicine.

In our study, the percentage of missed treatment was 17.1% in the one year between April, 2020 and March, 2021. Kahraman et al. (11) showed by a questionnaire that 35 out of 75 LSD patients had missed treatment sessions. Their study was based on data from the first nine months of the pandemic.

The patient's fear of infection and uncertainty regarding the pandemic may have reduced the patients' visits to the hospital for treatment. In a survey study considering the effect of COVID-19 on patients with rare metabolic diseases, it was reported that almost half of the patients missed their ERT, and the most important reason for this interruption in treatment was the fear of going to the hospital and becoming infected (14).

Our study found that treatment skipping rates were lower in the patients in our study than in the literature. This indicates that telemedicine has a positive effect on adherence to treatment. Compliance with treatment was increased via repeated telemedicine in those patients with poor compliance.

Curfews were imposed at intermittent periods to prevent any unfavorable effects of the pandemic worldwide. There were curfews in Turkey in the months of March, April, May, June, October, and November in

2020. In the periods including these months, the rate of disruption in treatment was the highest (April-May-June was 23.6%, October-November-December was 19.7%). Due to curfews, it may be the case that patients do not come to the hospital because of anxiety. Those patients with chronic diseases were more anxious during the pandemic, and so avoided hospital visits (15-17). A decrease in treatment skipping rates was noted in the following months. The effect of telemedicine may have increased adherence to treatment. On the other hand, treatment disruption may have led to a lack of healthcare access in the months of government-enforced curfews and then improved in the other months due to improved access.

There was no significant difference between male and female patients regarding treatment adherence. The treatment disruption rate in patients under 18 years was lower than those over 18 years. This may be due to the fact that the parents take charge in compliance with the treatment for their children even during a pandemic. In other words, the fact that skipping treatment under the age of 18 is lower than that of adults may be associated with the higher observance of parents with their children's treatment.

Andrade-Campos et al. (12) reported the impact of the COVID-19 pandemic on Gaucher patients. They reported that 25% of the patients skipped treatment, which is similar to our study. MPS patients have severe comorbidities such as narrow airways and respiratory problems. Therefore, the risk of COVID-19 infection in MPS patients is expected to be higher compared to Gaucher patients (18). The treatment compliance of MPS and Gaucher patients was considered in terms of this situation. However, there was no significant difference between the two groups in our study.

Clinical worsening in LSD patients has been reported in the literature due to treatment discontinuation (19,20). In our study, the comorbidity experienced in patients whose ERT was disrupted was not evaluated. During the telemedicine interviews, we learned that a patient with MPS IVA deteriorated clinically. The 14-year-old male patient had a disruption in treatment of 25% during the pandemic period (March, 2020-September, 2020). He complained of an inability to walk during this period of disruption of treatment. The patient's 6-minute walking test was recorded at 325 meters in 2019. When the patient was evaluated, the diameter of the foramen magnum, which had been 10 cm in a cranial MRI performed in 2019, narrowed to 0.7 cm in September, 2020. The urinary glucosaminoglycan

level can level, which had been 78 mg/gr creatinine (<60) in 2019, increased to 135 mg/gr creatinine (<30) in September, 2020. It was observed that the clinical and laboratory findings were further exacerbated in this period when 25% of the treatment was interrupted for this patient.

Sechi et al. (8) reported that 49% of patients receiving ERT in hospitals experienced interruption, versus 6% of patients treated at home. In many European countries, home-based treatment is carried out under COVID-19 pandemic conditions for ERT compliance (21). Home-based ERT is not available in Turkey. Home-based ERT may be an option which can increase the compliance rates of LSD patients with treatment during the COVID-19 pandemic (19,22).

Study Limitations

There were some limitations in our study due to it being a single-center experience for only one year. Further studies with larger populations and long-term results may provide more data about ERT adherence with telemedicine.

Conclusion

In conclusion, telemedicine could be a good option for follow-up, management, and to ensure continuity of treatment of LSD patients in pandemic periods. Also, switching to home-based ERT may be an option which can increase treatment compliance for LSD individuals. The continuity of treatment of LSD patients is crucial in order to prevent comorbidities.

Ethics

Ethics Committee Approval: Ethics Committee approval was obtained from the Local Ethics Committee of Ege University (21-11.1T/43).

Informed Consent: All patients or their parents included in this study gave informed consent to take part in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Y.Ç., Concept: M.Y.Ç., H.Y., F.E., S.K.U., M.Ç., Design: M.Y.Ç., Data Collection or Processing: M.Y.Ç., Analysis or Interpretation: M.Y.Ç., E.C., Literature Search: M.Y.Ç., E.C., Writing: M.Y.Ç., E.C.

Conflict of Interest: No conflict of interest is declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *Int J Surg* 2020; 76:71-6.
2. Cakir B. COVID-19 in Turkey: Lessons Learned. *J Epidemiol Glob Health* 2020; 10:115-7.
3. Ademhan Tural D, Emiralioglu N, Tural Hesapcioglu S, et al. Psychiatric and general health effects of COVID-19 pandemic on children with chronic lung disease and parents' coping styles. *Pediatr Pulmonol* 2020; 55:3579-86.
4. Portnoy J, Waller M, Elliott T. Telemedicine in the Era of COVID-19. *J Allergy Clin Immunol Pract* 2020; 8:1489-91.
5. Sun A. Lysosomal storage disease overview. *Ann Transl Med* 2018; 6:476.
6. Akar HT, Karaboncuk Y, Çıkkı K, et al. COVID-19-related anxiety in phenylketonuria patients. *Turk J Pediatr* 2021; 63:790-800.
7. Fiumara A, Lanzafame G, Arena A, et al. COVID-19 Pandemic Outbreak and its Psychological Impact on Patients with Rare Lysosomal Diseases. *J Clin Med* 2020; 9:2716.
8. Sechi A, Macor D, Valent S, et al. Impact of COVID-19 related healthcare crisis on treatments for patients with lysosomal storage disorders, the first Italian experience. *Mol Genet Metab* 2020; 130:170-1.
9. Elstein D, Giugliani R, Muenzer J, Schenk J, Schwartz IVD, Anagnostopoulou C. Impact of the COVID-19 pandemic on the standard of care for patients with lysosomal storage diseases: A survey of healthcare professionals in the Fabry, Gaucher, and Hunter Outcome Survey registries. *Mol Genet Metab Rep* 2021; 28:100788.
10. Zubarioglu T, Hopurcuoglu D, Uygur E, et al. The Impact of Telemedicine for Monitoring and Treatment of Phenylketonuria Patients on Metabolic Outcome During Coronavirus Disease-19 Outbreak. *Telemed J E Health* 2022; 28:258-65.
11. Kahraman AB, Yıldız Y, Çıkkı K, et al. Invisible burden of COVID-19: enzyme replacement therapy disruptions. *J Pediatr Endocrinol Metab* 2021; 34:539-45.
12. Andrade-Campos M, Escuder-Azuara B, de Frutos LL, Serrano-Gonzalo I, Giraldo P; GEEDL; FEETEG; AEEFEG. Direct and indirect effects of the SARS-CoV-2 pandemic on Gaucher Disease patients in Spain: Time to reconsider home-based therapies? *Blood Cells Mol Dis* 2020; 85:102478.
13. Bashshur R, Doarn CR, Frenk JM, Kvedar JC, Woolliscroft JO. Telemedicine and the COVID-19 Pandemic, Lessons for the Future. *Telemed J E Health* 2020; 26:571-3.
14. Lampe C, Dionisi-Vici C, Bellettato CM, et al. The impact of COVID-19 on rare metabolic patients and healthcare providers: results from two MetabERN surveys. *Orphanet J Rare Dis* 2020; 15:341.
15. Organization WH. Mental health and psychosocial considerations during the COVID-19 outbreak, 18 March 2020. World Health Organization; 2020.
16. Ayhan Başer D, Çevik M, Gümüştakim Ş, Başara E. Assessment of individuals' attitude, knowledge and anxiety towards COVID-19 at the first period of the outbreak in Turkey: A web-based cross-sectional survey. *Int J Clin Pract* 2020; 74:e13622.
17. Olgaç A, Kasapkara ÇS, Açıkel B, Yıldız Y, Molla GK, Kılıç M. The COVID-19 Pandemic and Enzyme Replacement Therapy in Lysosomal Storage Disorders. *J Pediatr Res* 2021; 8:370-6.

18. Ramaswami U, D'Amore S, Finnegan N, Hughes D, Kazemi M; Lysosomal Disorders Team, Royal Free London NHS Foundation Trust. Impact of SARS-CoV-2 (COVID-19) pandemic on patients with lysosomal storage disorders and restoration of services: experience from a specialist centre. *Intern Med J* 2021; 51:1580-93.
19. Politei J. Fabry disease during the COVID-19 pandemic. Why and how treatment should be continued. *Mol Genet Metab* 2020; 130:227-9.
20. Politei J, Porrás-Hurtado GL, Guelbert N, Fainboim A, Horovitz DDG, Satizábal JM. Enzyme replacement therapy interruption in mucopolysaccharidosis type IVA patients and its impact in different clinical outcomes. *JIMD Rep* 2021; 58:104-13.
21. Nowicki M, Bazan-Socha S, Kłopotowski M, et al. Considerations for Home-Based Treatment of Fabry Disease in Poland during the COVID-19 Pandemic and Beyond. *Int J Environ Res Public Health* 2021; 18:8242.
22. Kuzstal M, Kłopotowski M, Bazan-Socha S, et al. Is home-based therapy in Fabry disease the answer to compelling patients' needs during the COVID-19 pandemic? Survey results from the Polish FD Collaborative Group. *Adv Clin Exp Med* 2021; 30:449-54.