



# The COVID-19 Pandemic and Enzyme Replacement Therapy in Lysosomal Storage Disorders

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## ABSTRACT

**Aim:** The coronavirus disease-2019 (COVID-19) pandemic has caused a worldwide public health emergency, especially affecting people with chronic illnesses including lysosomal storage disorders (LSDs). The unfavorable conditions due to COVID-19 have mostly affected people with chronic conditions, in terms of disease vulnerability and access to health-care. In the present study, we aimed to assess the problems the patients with LSDs on enzyme replacement therapy (ERT) have encountered during the pandemic, and their level of anxiety. Parental evaluation has also been made for pediatric patients.

**Materials and Methods:** A total of 19 participants were recruited. A semi-structured interview was structured to evaluate the effects of the COVID-19 pandemic on ERT. The Turkish version of "Hospital Anxiety and Depression scale" (HADS) for adult patients and parents were used to evaluate anxiety. Patients between ages 8-17 completed the child version of the Revised Child Anxiety and Depression scale (RCADS).

**Results:** The study was completed by 19 patients, and 13 parents. Five patients (26%) admitted temporary disruption of treatment, of which the most common reason was the fear of getting infected. Eighty-nine percent of all participants were willing to receive treatment at home. Only one adult patient revealed to feel anxiety (16%). While among parents evaluated with HADS, 7/13 had scores that indicated depression and anxiety, 3/4 pediatric patients had RCADS scores indicative of anxiety and depression.

**Conclusion:** The problems LSD patients have been facing during the pandemic, should be identified along with their attitudes regarding ERT in order to maintain the sustainability of their treatment. The psychological health of these patients should also be identified and supported, to provide optimal care to patients.

**Keywords:** COVID-19, lysosomal storage disease, enzyme replacement therapy, home-therapy

## Introduction

The coronavirus disease-2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has become a global problem, affecting nearly every country since March 2020 (1). Along with increasing cases and unavailability of a specific treatment, the health systems of countries have become

overloaded with the burden of the pandemic. The disease has caused increased anxiety worldwide, also in children, due to the fear of getting infected, and suffer its severe complications.

The unfavorable conditions due to COVID-19 have mostly affected people with chronic conditions, in terms of disease vulnerability and access to health-care (2). Patients who

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are dependent on health-care facilities on a routine basis, have faced several problems due to restrictions concerning treatment and follow-up visits, since most of the hospitals have been focused on the treatment of the patients severely affected with SARS-CoV-2. Also, due to the fact that these patients are obliged to attend health-care facilities, the risk to get infected by the COVID-19 pandemic has increased (3).

People with rare metabolic disorders are also under risk during the pandemic because of multi-systemic involvement including vital organs (4). Lysosomal storage diseases (LSDs), are a group of rare, inherited metabolic disorders, that are characterized by progressive accumulation of non-digested substrates within cells, due to diminished activity of lysosomal enzymes. Although they cannot be cured, some treatment options have been emerged by the advances in the field. Enzyme replacement therapy (ERT) is administered as intravenous infusions, for every 1-2 weeks, and has been successful in many LSDs. Although hematopoietic stem cell transplantation and substrate reduction therapy (SRT) are available for a limited number of LSDs, ERT is the only approved and most effective therapy for the majority for now, and requires lifetime administration due to short half-life (5).

At the present time, Gaucher, Fabry, Pompe diseases, acid lipase deficiency, as well as mucopolysaccharidoses (MPSs) type I, II, VIa, VI and VII can be treated by ERT (Table I) (6). Although many centers provide the facilities for home-based infusions for these patients, in some countries patients need to attend hospitals to receive treatment, as in Turkey.

In the present study, we aimed to evaluate the problems regarding treatment of patients with LSDs on ERT during the COVID-19 pandemic. We have also assessed the anxiety levels of patients and parents related with the pandemic, using validated depression scales.

## Materials and Methods

The study was carried on between September and October 2020. Patients with LSDs that were receiving ERT in University of Health Sciences Turkey, Dr. Sami Ulus Maternity and Child Health Training and Research Hospital were invited to participate in the study. A semi-structured interview was designed on the attitudes of patients or their parents regarding the COVID-19 pandemic. Also, the difficulties that the patients experienced during hospital admission and access to medication were evaluated. Parents were asked to complete a set of questions including

age, sex, duration of ERT, the presence of COVID-19 infection within the family or relatives, contact with a COVID-19 patient, adherence to the restrictions due to the pandemic, and any problems encountered during hospital admissions for ERT or access to medications (Table II).

To assess depressive symptoms of patients between ages 7-18, Revised Children's Anxiety and Depression scale (RCADS), and patients above the age 18, and for parental evaluation, the "Hospital Anxiety and Depression scale" (HADS) were used. Both of these questionnaires have been shown to be a reliable and valid tool to assess the general population (7).

The RCADS consists of 47 items developed to evaluate DSM-IV based symptoms of anxiety disorders and depression in children and adolescents, and their parents, with response options of 0= never, 1=sometimes, 2=often, and 3=always (7). The questionnaire was validated in Turkish by Gormez et al. (8,9). The answers of the questionnaire are grouped into six subscales: Separation Anxiety Disorder, Anxiety Disorder (General Anxiety Disorder), Social Phobia, Panic Disorder, Major Depressive Disorder, and Obsessive Compulsive Disorder. For each subscale, scores are given, as well as a total anxiety score, which is the sum of all anxiety, and a total score for all the scales (sum of six subscales). Higher score indicates greater depressive symptoms. Raw scores are converted to age and gender adjusted T scores, using standardized tools (7).

LSD subtype	ERT
Gaucher disease	Imiglucerase Taliglucerase Velaglucerasa alfa
Fabry disease	Agalsidase alpha Agalsidase beta Pegunigalsidase alpha
MPS I (Hurler-Scheie syndrome)	Laronidase
MPS II (Hunter syndrome)	Idursulfase Idursulfase beta
MPS IVa (Morquio A syndrome)	Elosulfase alpha
MPS VI (Maroteaux-Lamy syndrome)	Galsulfase
MPS VII (Sly syndrome)	Vestronidase alpha
Acid lipase deficiency	Sebelipase alpha
Pompe disease	Alglucosidase alpha
Alpha-mannosidosis	Velmanase alpha

ERT: Enzyme replacement therapy, LSD: Lysosomal storage disorders, MPS: Mucopolysaccharidose

**Table II.** Questions of the semi-structured interview on the attitudes of patients regarding ERT during the pandemic

Age:
Sex:
Patient      Parent
Diagnosis:
Duration of ERT: ..... years
Have you or your child been diagnosed to be infected with COVID-19? Yes <input type="checkbox"/> No <input type="checkbox"/>
Have you felt anxiety regarding the COVID-19 pandemic? Yes <input type="checkbox"/> No <input type="checkbox"/>
Have you adhered to the restrictions regarding the COVID-19 pandemic? Yes <input type="checkbox"/> No <input type="checkbox"/>
Have you (or your child) had any interruptions of enzyme replacement therapy during the COVID-19 pandemic? Yes <input type="checkbox"/> No <input type="checkbox"/>
Have you ever felt anxiety during at the hospital during receiving enzyme replacement therapy regarding the COVID-19 pandemic? Yes <input type="checkbox"/> No <input type="checkbox"/>
Have you ever felt anxiety during transportation to hospital for enzyme replacement therapy regarding the COVID-19 pandemic? Yes <input type="checkbox"/> No <input type="checkbox"/>
Have you ever felt anxiety during attending pharmacies for drug supply regarding the COVID-19 pandemic? Yes <input type="checkbox"/> No <input type="checkbox"/>
Did you have any treatment interruptions during the COVID-19 pandemic? Yes <input type="checkbox"/> No <input type="checkbox"/> If so, which of the following items describes the reason for treatment interruption? a) Fear for myself (or my child) to get infected at the hospital b) Fear for myself (or my child) to get infected during transport to hospital due to using public transportation c)The hospital I / my child is receiving therapy are too occupied with COVID-19 patients
COVID-19: Coronavirus disease-2019, ERT: Enzyme replacement therapy

Hospital Anxiety and Depression scale (HADS) consists of 14 items divided into two subscales for anxiety and depression (7 depressive and 7 anxiety items). The items are rated on a 0-3 scale, where each items are summed to reach a total score. A score of  $\geq 10$  indicates anxiety, where  $\geq 7$  indicates depression (10). It is validated to be used in adolescents, and has suitable psychometric properties for this population (11).

The questionnaires were conducted in a private room by patients and parents and took about 5 minutes to complete. Patients that did not attend our clinic during the study period completed the survey via telephone. All participants provided informed consent.

Ethics approval was obtained from the ethics committee of Ankara Yıldırım Beyazıt University, on September 2020, from the local institutional review board according to guidelines of the Helsinki Declaration of Human Rights.

## Results

At the time of the study, 22 LSD patients being followed-up in our department, were on ERT, and thus regularly admitted to the outpatient clinic, 19 of whom accepted to participate in the study. The study was completed with 19 patients (13 pediatric and 6 adult patients) and 13 parents.

The ages of pediatric patients at ranged from 2.5 to 16 years (mean age:  $7.7 \pm 4.7$  years). Male to female ratio was

(7/6). Ages of adult patients ranged from 19 to 50 years (mean age:  $35.2 \pm 14.1$ ) (male to female ratio: 4/2). Thirteen parents were also evaluated, ages ranging between 27 and 44 years (mean age  $33.8 \pm 5.98$ ), and male to female ratio being 4/9. The demographic data of patients are given in Table III. All patients were receiving ERT (alglucosidase alfa, laronidase, idursulfase, galsulfase, imiglucerase, taliglucerase alfa, agalsidase alfa, oragalsidase beta, according to diagnosis). The patients were receiving ERT for 1 to 14 years. Mean duration of ERT was  $4.5 \pm 3.2$  years (Table III).

None of the patients had a proven diagnosis of an infection with COVID-19. All patients indicated that they complied with the precautions that were being taken by the ministry of health. Three patients revealed getting into contact with a person diagnosed with COVID-19 from relatives, but had no signs of infection.

Five patients (26%) admitted temporary disruption of treatment. Four of these patients were continuing ERT at longer intervals (once a month). The most common reason was the fear of getting infected at the hospital, or during transport to hospital due to using public transportation. One patient had missed one infusion on March 2020, due to inadequacy of hospital services dealing with the burden of COVID-19 (Table IV). Eighty-nine percent of participants were willing to receive their treatment at home during the pandemic, other than two patients, one the parent of a child

**Table III.** Demographic characteristics of patients enrolled in the study

Demographic characteristics	Patients	Parents
Age (mean ± SD)		
Pediatric	2.5-16 years (7.7±4.7 years)	
Adult	19-50 years (35.2±14.1)	27-44 years (33.8±5.98)
Sex		
Pediatric		
Male	7	
Female	6	
Adult		
Male	4	4
Female	2	9
Duration of ERT (mean ± SD)	4.5±3.2 years	
Subtype of LSD (n)		
Fabry disease	6	
Gaucher disease	3	
MPS 1	2	
MPS 2	2	
MPS 6	2	
Pompe disease	4	
ERT: Enzyme replacement therapy, LSD: Lysosomal storage disorders, MPS: Mucopolysaccharidose, SD: Standard deviation		

**Table IV.** The reasons of disruption of treatment

Reason of disruption	(n)
Fear of getting infected at the hospital	4
Fear of getting infected during transport to hospital	4
Hospital services loaded with the burden of COVID-19	1
COVID-19: Coronavirus disease-2019	

with Pompe disease who had a history of anaphylaxis during treatment and an adult Fabry patient due to a personal feeling (fear of allergic reaction).

Nine out of thirteen parents claimed to feel anxiety during hospital admissions or regarding drug supply (69%), among them, 7 (53%) had HADS scores that indicated depression, and increased anxiety. Among the children of these parents, 3 had interrupted treatment during the pandemic, and the reason for interruption was the fear of getting an infection (Table V).

**Table V.** Anxiety and depression levels of patients and rate of treatment interruption

	Positive* (n)	Interruption of treatment among participants with increased anxiety and depression (n)
Claim of feeling anxiety during hospital admission for ERT		
<b>Patients</b>		
Adult	1/6	1
Pediatric	2/4	
<b>Parents</b>	9/13	
<b>HADS score</b>		
Adult patients	1/6	1
Parents	7/13	3**
<b>RCADS score</b>		
Patients (Aged 8-17)	3/4	2
*Indicating anxiety and depression **Indicates treatment interruption of children of these parents ERT: Enzyme replacement therapy, RCADS: Revised Child Anxiety and Depression Scale		

Among 6 adult patients, only one (who is also the mother of one pediatric patient) had scores indicative of anxiety and depression, who had also interrupted treatment. The same patient revealed to feel anxiety of getting infected during hospital admissions or at pharmacies (16%).

Among patients aged 8-17 that were evaluated by RCADS (4 patients), sub-scores of 3 patients (75%) were found to be above the threshold level and one of these 3 patients also had high total anxiety and depression scores. Two of these patients had also interrupted treatment due to fear of getting infected during receiving ERT.

### Statistical Analysis

Statistical analyses regarding the relationship between interruption of treatment and anxiety scores were not performed due to insufficient number of patients enrolled in the study.

### Discussion

The COVID-19 pandemic due to SARS-CoV-2 caused weaknesses in the world-healthcare systems of countries, pre dominating rare and chronic conditions including inborn errors of metabolism (1,2). Particularly, patients with inborn errors of metabolism (IEMs) can be considered at high risk for severe SARS-CoV-2 infection, since they often suffer

from a multisystem disease, including respiratory and cardiovascular system involvement (12).

It is well known that SARS-CoV-2 uses the lysosomal system to infect cells (13). Therefore, patients with LSD may be at increased risk for infection and complications of SARS-CoV-2, because of lysosomal dysfunction, and activation of inflammatory cascades (14).

Our study group consists of a vulnerable population, not only due to the effects of the disease itself, but also being dependent on health-care services in terms of treatment. Neither of our patients had a proven diagnosis of COVID-19. This may be due to the strict adherence of patients to the rules for prevention of infection. It is impossible to generalize our findings, since tests were not done on a routine basis, and asymptomatic cases could not be ruled out. Previous studies reported in the literature have also reported low incidence of COVID-19 among LSD patients (12,15).

Scarce amount of studies exist in the literature addressing LSD patients during the COVID-19 pandemic. Mistry et al. (14) have published guidelines for the management of Gaucher disease patients and have indicated that ERT should be continued regularly, and interruptions should not be extended, even in infected patients, to avoid aggravation of symptoms due to withdrawal of treatment and also support the vital organ systems, in case of infection. The authors have stated that, interruption of therapy for weeks to months could be tolerated in stable patients. Unfortunately, it is impossible to generalize these guidelines to other subtypes of LSDs, since each LSD is unique in its own clinical findings and progression.

A study by Andrade-Campos et al. (12) revealed that, among 48 Gaucher disease patients receiving hospital-based ERT, 11 (25%) reported therapy interruptions related with the outbreak, while patients on oral SRT continued to receive treatment regularly. Sechi et al. (16) have reported 102 patients with various types of LSDs, of whom 71 were receiving ERT during the pandemic. While, patients receiving home-based ERT continued their treatment regularly, disruptions occurred in 49% of patients receiving ERT in the health-care centers (16).

Unfortunately, home-therapy is not currently available in Turkey. Thus, all patients recruited in our study were on hospital-based treatment. The rate of interruption of treatment was 26% in our study, similar to the study reported by Andrade-Campos et al. (12). Obviously, our study population does not reflect the overall situation in our country. Turkey has been suffering from the devastating

effects of the pandemic, and the rate of interruption of treatment among LSDs may be much higher.

In a recent report, Elmonem et al. (4) have analyzed 16 centers taking care of IEMs during the COVID-19 pandemic. According to their report, 88% of centers have limited the numbers of routine patients' visits per day and 20% of have referred patients to other IEM clinics. Also, travel restrictions have affected the follow-up of patients of 93% of participating centers. The authors have specified the most important factor of treatment interruption to be the fear of the patient and the family from going to the hospital during a pandemic, and have suggested clear guidelines for patient management in each subgroup of IEMs to be prepared in such circumstances (4).

Since ERT is given with frequent intervals (weekly or bi-weekly), the obligation to attend health-care facilities regularly, is not only time consuming, but also is unmanageable during times of overloading to the health-systems. Home therapy should be encouraged in patients with stable conditions as LSDs, since it is an efficient and comfortable way to sustain treatment during pandemics. Another solution may be separation of specific centers for the care of patients with rare and chronic illnesses to be infusion centers, or sparing a safe area within centers for infusion. Since a shortage of health-care staff may also be present during an emergency state, developing protocols for the management of LSDs during pandemics is also necessary. Also, to ensure safe transport of patients to health centers may be helpful.

Several studies have shown that the COVID-19 pandemic has led to panic and anxiety in patients with chronic illnesses (17). Fiumara et al (18) have specifically analyzed the attitude of 15 patients with LSD towards the pandemic and the impact of the outbreak on their treatment. Parents of patients at pediatric ages were also involved in the study. Although no statistically significant difference was found compared to controls, all the evaluated persons revealed increase of anxiety related with COVID-19. The authors concluded that, the reactions of patients with LSD were qualitatively different than the general population, and they have stressed the fragility and isolation of such patients.

Similar to the studies in the literature, we have also determined depressive symptoms in the majority of our study group consisting of LSD patients and their parents. What is more interesting was that, a considerable number of parents with anxiety and depression, had interrupted their child's treatment, with the fear of getting infected. The same situation was observed among the adult patients,

in which the patient with HADS scores indicative of both anxiety and depression, was the one who interrupted treatment. Our study indicates that, increased anxiety, along with depression, may aggravate the fear related with the pandemic, and may contribute to withdrawal of ERT. Thus, the identification of patients with anxiety and depression may be useful, since LSDs represent a vulnerable group of patients. Patient organizations may also be helpful, a part of care and support. The patients should be encouraged for the continuation of treatment.

### Study Limitations

Our study has various limitations. First of all, a small number of patients were evaluated that may not reflect the whole population of LSDs that have been diagnosed and being treated in our country, and may not be generalized. Secondly, parental reports were evaluated for children under age 8 which may not directly reflect the child's own feelings.

### Conclusion

Patients with LSDs represent a vulnerable group of the population due to the multisystemic effects of the disease. It is important to identify the problems these patients have been facing during the pandemic, also their attitudes regarding ERT in order to maintain the sustainability of their treatment. There is an urgent need to introduce home-based treatment options, where unavailable, to reduce the unfavourable health impacts due to disruptions of treatment. Also, individual guidelines for subtypes of LSDs should be created for the treatment strategies during the pandemic. Home-based therapy should be a choice for suitable patients since the effects of the pandemic seem to continue for an unpredictable period of time. The psychological health of these patients should also be identified, where needed, to provide optimal care to patients.

### Ethics

**Ethics Committee Approval:** Ethics approval was obtained from the ethics committee of Yildirim Beyazit University, on September 2020 (number: 76).

**Informed Consent:** All participants provided informed consent.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: A.O., C.S.K, S.B.A., Y.Y., G.K.M., M.K., Concept: A.O., C.S.K, M.K., Design: A.O., C.S.K,

M.K., Data Collection or Processing: A.O., S.B.A, Y.Y., G.K.M., Analysis or Interpretation: A.O., S.B.A., Y.Y., M.K., Literature Search: A.O., S.B.A, Y.Y., G.K.M., Writing: A.O., C.S.K, S.B.A., Y.Y., G.K.M., M.K.

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