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Invisible burden of COVID-19: enzyme replacement therapy disruptions

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Abstract

Objectives: Lysosomal storage diseases (LSD) constitute an important group of metabolic diseases, consisting of approximately 60 disorders. In some types of lysosomal diseases, enzyme replacement therapy (ERT) is administered intravenously in weekly or biweekly doses. Unfortunately, scheduled ERT during COVID-19 was disrupted. We considered the possibility of adverse outcomes caused by the disruption in the treatment of patients with lysosomal storage disorders.

Methods: During the COVID-19 pandemic, we conducted a questionnaire that was delivered via Internet to assess how this vulnerable patient group was affected by the pandemic in terms of their access to treatment and their disease-related symptoms.

Results: The questionnaire was filled out by 75 patients. There were 35 patients whose treatment dose was missed because of COVID-19. The most common reason for skipping treatment was not wanting to go to the hospital for fear of contracting COVID-19. These 35 patients missed a median of four doses of ERT (range: 1–16 dosages). Twenty-one patients (60%) claimed that they were affected physically by not taking ERT (20 mucopolysaccharidoses, 1 Fabry disease), whereas 14 (40%) did not.

Conclusions: Interruption of ERT during the COVID-19 pandemic may have significant consequences. It may be beneficial to switch to home treatment or reserve dedicated facilities. With proper planning and management, the

treatment disruptions of this particular group can be avoided.

Keywords: COVID-19; disruptions; enzyme replacement therapy; lysosomal storage diseases; survey.

Introduction

In December 2019, an outbreak of pneumonia with unknown origin started in China's Hubei Province and it spread quickly all around the world [1]. The responsible agent was identified as a novel coronavirus (SARS-CoV-2) and the disease was named coronavirus disease 2019 (COVID-19). The World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020 [2].

As of 31 January 2021, while there were 103,294,500 confirmed cases worldwide, 74,930,190 people have recovered, and 2,232,901 patients have died due to the virus [3]. The pandemic has had a huge impact on the economy and health systems in many countries. The first case in Turkey was reported on 11 March 2020. Unlike other countries, to keep the economy alive, curfews were imposed only on weekends and traditional holidays. Intercity transportation was banned except for logistic support. Adults over the age of 65, who are the major high-risk group for mortality and severe morbidity, were prohibited from going out. Children under the age of 18 were also subject to a curfew to limit interfamilial spread. In addition, nonemergency cases were restricted to avoid collapsing of the health care system. Patients who did not experience respiratory distress were treated at home. Hospitals thus did not exceed their capacity. Although such precautions were carried out to prevent disruption of general health services, patients did not want to come to the hospital out of fear of contracting COVID-19, especially before July 2020 [4].

The course of COVID-19 in children is different from that in adults. The hospitalization rates of children are significantly lower, compared to adults with COVID-19 [5]. This suggests that children may have less severe COVID-19 [6]. The clinical spectrum may range from asymptomatic children to mild upper respiratory or gastrointestinal tract symptoms to severe conditions, such as multisystem

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inflammatory syndrome associated with COVID-19 (MISC). However, data is sparse in children, especially in children with inborn errors of metabolism. These diseases are rare on an individual basis but collectively constitute a significant burden, as they occur in 1 out of 1,800–2,500 live births [7, 8]. Lysosomal storage diseases (LSD) constitute an important group of metabolic diseases, consisting of approximately 60 disorders, characterized by the storage of substrates in lysosomes due to impairment in the activities or transport of lysosomal enzymes or to defects in the receptor proteins of lysosomal membranes [9]. LSDs are further classified into sphingolipidoses (e.g. Gaucher disease, Fabry disease), gangliosidoses, mucopolysaccharidoses (MPS), oligosaccharidoses, etc., depending on the major accumulating substance. The estimated incidence of LSD overall is 1/5,000 [10]. They are characterized by chronic, progressive, and multisystem involvement, and the age of onset of the disease may vary from the fetal period to adulthood.

In some types of LSD, enzyme replacement therapy (ERT) is administered intravenously in weekly or biweekly doses. For some types of MPS, ERT has been shown to improve respiratory and cardiac function, alleviate organomegaly, improve range of motion, and provide a better health-related quality of life [11]. Enzyme replacement therapy in Pompe disease (glycogen storage disease type 2) improves cardiomyopathy and cardiac functions [12]. It has been shown that it can reduce neuropathic pain and alleviates gastrointestinal symptoms and improves pulmonary functions in Fabry disease, while in Gaucher disease, significant improvement in organomegaly and hematological parameters is observed [13–16]. Unfortunately, scheduled ERT during COVID-19 was disrupted [17]. It can be said that children and adults with IEM may be at high risk in the COVID-19 pandemic as their immune systems are more vulnerable [18]. Lysosomal storage diseases are considered to be high risk also because of respiratory, renal, and cardiac involvement [19]. We considered the possibility of adverse outcomes caused by the disruption in the treatment of patients with lysosomal storage disorders. During this pandemic, we conducted a questionnaire to assess how this vulnerable patient group was affected by the pandemic in terms of their access to treatment and of their disease-related symptoms.

Materials and methods

Study design and participants

This cross-sectional, observational study was carried out at the Pediatric Metabolism Unit of Hacettepe University İhsan Doğramacı

Children's Hospital and was approved by Hacettepe University Ethics Committee for Non-Interventional Clinical Studies (June 2020, GO 17/821). According to the data in the registry system of our center, 92 patients with MPS, five patients with Gaucher disease, nine patients with Pompe disease, and 10 patients with Fabry disease were receiving ERT as of July 2020. Among these patients, those willing to participate in the study were included.

Data collection

In order to adhere to the social distancing efforts, patients in our center were contacted via telephone or social media, and questionnaire forms were delivered via Google Forms to the eligible patients, and data was collected from the forms filled and submitted back by the patients anonymously. The questionnaire (see Supplementary Material) included questions about sociodemographics, characteristics of ERT, and social influence of COVID-19. The online questionnaire was sent out on 1 July 2020, and data collection was terminated on 1 October 2020.

Statistical analyses

The data were analyzed by the SPSS v22.0 (SPSS Inc, Chicago, IL). Descriptive statistics were presented as mean $\pm$ standard deviation, median (minimum-maximum), and frequencies. For determination of the normality of the distributions, Kolmogorov-Smirnov or Shapiro-Wilkson tests were used, where appropriate. The level of statistical significance was accepted as $p < 0.05$.

Since the numbers of missed doses were not distributed normally, the Mann-Whitney U test was used in comparing qualitative characteristics among affected and not affected patients. Numbers of missed doses with the affected state were analyzed using receiver operating characteristic (ROC) curves. Fisher's exact test was used to compare proportions in adversely affected disease groups.

Results

Analysis of the questionnaire results

The questionnaire was filled out by 75 patients. Patient characteristics are shown in Table 1 and Supplementary Material. For ERT, patients had been prescribed laronidase, idursulfase, elosulphae alfa, galsulphae, alglucosidase alfa, agalsidase beta, or imiglucerase for MPS-I, MPS-II, MPS-IVA, MPS-VI, Pompe disease, Fabry disease, or Gaucher disease, respectively. The median duration of ERT was five years (1–15 years). The median number of people living in the same household (median family size) was four people (range: 2–9). Patients traveled a median of 10 km (1–50 km) for ERT. There were 35 patients whose treatment dose was missed because of COVID-19. These 35 patients missed a median of four doses of ERT (range: 1–16 doses). The reasons (fear, transport, access, hospital room

problem) for skipping treatment of these 35 patients were evaluated within themselves. Six patients marked more than one option. Twenty-one of them (60%) claimed that they were affected by not taking ERT (20 mucopolysaccharidoses, 1 Fabry disease), whereas 14 patients (40%) did not. Treatment features are shown in Table 1. Patients' responses for how they were affected by not taking ERT are shown in Figure 1. Eight participants had marked more than one option. Twenty-nine patients (82.9%) received their treatment, as usual, 4 (11.4%) needed to change the hospital, two patients (5.7%) shifted to home therapy. No patient was affected by COVID-19. Questions about social effects and COVID-19 – related questions are shown in Table 2.

The best cut-off value for the number of missed doses that lead to worsening of symptoms was detected as two or three doses (Figure 2 and Table 3). The median number of missed doses was 4 (2–16) in affected patients vs. 1 (1–7) in nonaffected patients ($p < 0.001$). The distribution of affected and unaffected patients among those with treatment disruptions is shown in Table 4. There were statistically significant differences regarding being affected by treatment disruption across disease groups.

Overview of free-text comments

The questionnaire included a section wherein the participants were asked to write any comments regarding the problems they faced related to ERT amidst the COVID-19 pandemic if they chose to. Eight participants expressed their gratitude for conducting this questionnaire. Six wrote that they were experiencing financial difficulties and that they lost their jobs. Three stated that they wanted to receive ERT at home, but it was not available. One participant asked that information about the impact of COVID-19 on MPS patients be provided on social media. One participant stated that they could not obtain their ERT doses because their medicine report had expired. Other free text answers included:

“Life is so hard and cruel.”

“It is scary enough on its own, but for families with special children like us, living with fear every day is a nightmare.”

“During this process, being able to receive ERT was not the only problem. Not being able to move, to go to school, to physical therapy, which made it more difficult to walk, were also problems. Granting administrative leave to families of children with special needs is also a topic worthy of discussion.”

Table 1: Patient characteristics and treatment features.

<i>Patient age, years, median (min-max)</i>	12 (2–58)	
<i>Gender n, %</i>	M 44 (58.7)	
	F 31 (41.3)	
<i>Diagnoses n, %</i>		
Mucopolysaccharidosis	65 (86.7)	
type I	6 (8)	
type II	2 (2.7)	
type IVA	33 (44)	
type VI	24 (32)	
Fabry disease	7 (9.3)	
Pompe disease	2 (2.7)	
Gaucher disease	1 (1.3)	
	n	%
<i>Frequency of taking enzyme</i>		
Weekly	64	85.3
Biweekly	11	14.7
<i>Receiving drug treatment where they live</i>		
Yes	67	89.3
No	8	10.7
<i>Changes on ERT location</i>		
Change of hospital	10	13.3
Shift to home therapy	10	13.3
No change	55	73.3
<i>Disruption of treatment</i>		
No	40	53.3
Yes	35	46.7
<i>The reason for disruption (n=35)</i>		
Being afraid to go to the hospital	26	74.3
Not acquiring the medicine	6	17.1
Transportation problem to go to the hospital	2	5.7
No hospital beds because of COVID-19 patients	7	20
<i>Adversely affected by disruption of ERT (n=35)</i>		
Yes	21	60
No	14	40
<i>Difficulty in accessing medication</i>		
Yes	6	8
No	69	92

Figure 1: Symptoms reported by the patients after interruption of enzyme replacement therapy.

Table 2: COVID-19 – related questions.

	n	%
<i>How COVID 19 affected your life</i>		
Very negatively affected	25	47.2
Slightly negatively affected	18	34
Not effected	10	13.3
<i>How COVID-19 affected the lives of other family members</i>		
Very negatively affected	27	45
Slightly negatively affected	23	38.3
Not effected	10	13.3
<i>Distribution of the sources from which patients received information during the COVID-19 pandemic</i>		
Television broadcasts	67	89.3
Physician's opinion	13	17.3
Internet broadcasts	25	33.3
Family members	20	26.7
Friends	4	5.3
<i>Was anyone living in the same house diagnosed with COVID-19?</i>		
Yes	1	1.4
No	72	98.6
<i>Do you follow the rule of staying at home?</i>		
I comply fully	52	69.3
I rarely go out (for example: Only for the market)	21	28
I do not follow the rule of staying at home	2	2.7
<i>Do you think that your risk of severe COVID-19 is increased?</i>		
Yes	53	70.7
No	6	8.0
I do not know	16	21.3

Table 3: Sensitivity and specificity values for missed ERT doses leading to worsening of symptoms (derived from ROC curve in Figure 2).

Number of missed ERT doses	Sensitivity, %	Specificity, %
2	90.5	85.7
3	85.7	85.7
4	47.6	92.9

ERT, enzyme replacement therapy.

Table 4: Proportions of adversely affected and nonaffected patients in ERT-disrupted group.

Diagnosis	Number of patients with ERT disruption	Affected n, %	Nonaffected n, %
MPS I	4	2 (50.0)	2 (50.0)
MPS IVA	19	10 (52.6)	9 (47.4)
MPS VI	11	8 (72.7)	3 (47.3)
Fabry disease	1	1 (100)	–

There were no statistically significant differences regarding the proportion of patients being affected from ERT disruption amongst the different lysosomal storage disorders (MPS I vs. MPS IVA [$p=1.000$], MPS IVA vs. MPS VI [$p=0.560$] and MPS I vs. MPS VI [$p=0.442$]). ERT, enzyme replacement therapy.

Discussion

While the COVID-19 pandemic rages on, our health system and patients are experiencing difficult times. The health system has been fighting COVID-19 while it is struggling to prevent the disruption of general health services. We evaluated the causes of ERT disruption in lysosomal storage diseases and the personal consequences of this interruption.

In this study, we found that the most important reason for the disruption of our patients' ERT was fear of going to the hospital and contracting the infection. In the study conducted by Sechi et al. the most important reason for ERT disruption was fear of going to the hospital, which is similar to our study [17]. The second reason was unprepared hospitals with low capacities and insufficient arrangements at the beginning of the pandemic.

Almost half of our patients missed their ERT. It was revealed that they had some complaints such as psychological problems or somatic effects like gait disturbance, shortness of breath, joint pain, and weakness. It seems that patients were willing to be at risk of these effects to avoid getting COVID-19. The effects of ERT interruption in MPS

Figure 2: ROC curve for the number missed doses leading to reported worsening of symptoms. Area under the curve=0.92, 95% confidence interval: 0.818–1.000, $p<0.001$.

may be visceromegaly, deterioration in respiratory function, and walking capacity, which are consistent with the findings of our study [20, 21]. It is known that ERT is beneficial for joint pain and decreases the pain score. After ERT is discontinued, there may be a faster deterioration than the natural disease course. When starting ERT, there is a decrease in accumulated GAG compounds, which subsequently reverses the inhibition of GAG synthesis. Hence the sudden interruption of the ERT leads to a faster GAG accumulation than before [22]. Due to all these reasons, discontinuation of ERT is expected to have negative clinical consequences.

As a solution to these problems, some patients have started home treatment. In the study conducted by Sechi et al. the home treatment rate was 16% [17]. When the thoughts of our patients were questioned, some mentioned that they wanted to receive home infusions. In our country, home health care services can be provided entirely by the personnel who are allocated by the local government. It can vary according to the density of the hospital and the requirement of staff. If it is a center that cannot provide health care at home, improvement of infusion centers can prevent interruption. This is the most effective solution for maintaining access to treatment in terms of not disrupting general health services for now. Certainly, these homecare teams are recommended to do this by paying attention to reasonable personal protective equipment and precautions. On a separate note, the patients' fear of going to the hospital, which is the major contributor to treatment interruption in our study, can only be overcome with proper implementation and explanation of the infection control measures together with better overall local and national control of the pandemic.

The vast majority of our patients think that their risk of severe COVID-19 is higher than the general population. The guideline prepared by the British Inherited Metabolic Diseases Group indicates inborn errors of metabolism with underlying respiratory problems as high risk in the COVID-19 outbreak [19]. Interestingly, Pierzynowski et al. suggest that patients with mucopolysaccharidosis are less susceptible to SARS-CoV-2, based on transcriptomic analyses. In other words, it has been hypothesized that the genetic defect may create an unfavorable environment for the virus to reproduce [23]. In this instance, it may be controversial that these diseases may be a high risk for COVID-19. However, it is well known that anatomical and physiological changes forming thick mucus due to GAG storage increase susceptibility to infectious agents, and disruption of ERT can aggregate the frequency of infection [24].

We evaluated that our patients learned most of their information about COVID-19 from media channels such as the Internet and television. In the study conducted in Italy on the psychological effect of the COVID-19 pandemic on lysosomal diseases, it was revealed that patients were living with anxiety and uncertainty fed by continuous media updates [25]. In a Youtube based study analyzing the most commonly viewed Turkish and English videos regarding the pandemic, only 37.5% were determined to be helpful video content [26]. We demonstrated in our study that these concerns were reinforced by the fears of in-hospital transmission, causing the enzyme disruption. It suggests that it may be important to use the media effectively during the epidemic. The fact that one of our patients asked for information about COVID-19 on social media in her response showed once again that social media is an effective tool in directing people.

Our study has limitations. Since the questionnaires were not filled in by face-to-face interviews and patients or their parents were asked to fill in the questionnaire, it is not known whether the responders fully understood the questions. As the completed questionnaires were returned anonymously, the researchers were blinded to the participants' identities, making it impossible to correlate the responses with clinical data. The data were limited to the participant's subjective self-report, which may be biased. We could not perform objective tests (such as respiratory function tests, endurance tests, or urine glycosaminoglycan levels) to evaluate disease progression.

Conclusion

Apart from the purpose of obtaining information for this study, we were moved by our observation that the mere "virtual" contact with the family made an impact during this pandemic. For example, one patient's parents stated that they could not take the drug because they could not renew the drug prescription at the local health center. To decrease the burden on the health care system, the Ministry of Health had renewed the prescriptions of drugs used for chronic illnesses, and the patient did not have to travel to the health center to receive the prescription, but the family was not aware of this new regulation. We shared this information when we reached the family by phone to deliver the survey. So the patient had the opportunity to obtain the drug. In addition, free text answers (see Overview of free-text comments) underlined the psychosocial burden of having LSD during these unprecedented times. Many of our patients thanked us for organizing this questionnaire. The participants expressed their gratitude to the health care professionals. For this reason, especially when face-to-face

visits are not possible, regular phone calls from the metabolic centers may help the patients and their families to feel that there is a cooperation between the doctor and the patient and that they are not alone.

In conclusion; interruption of ERT during the COVID-19 pandemic may have significant consequences. It may be beneficial to switch to home treatment and improve telemedicine applications. With proper planning and management, the treatment disruptions of this particular group can be avoided. During this pandemic, more data should be collected about this rare patient group.

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Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The study was approved by Hacettepe University Ethics Committee for Non-Interventional Clinical Studies (June 2020, GO 17/821).

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