The Effects of The COVID-19 Pandemic on Patients With Lysosomal Storage Disorders in Israel

Eyal Kristal

Soroka Hospital: Soroka Medical Center

Ben Pode-Shakked

Edmond and Lily Safra Children's Hospital

Guy Hazan

Soroka Hospital: Soroka Medical Center

Ehud Banne

Wolfson Medical Center: Edith Wolfson Medical Center

Galina Ling

Soroka Hospital: Soroka Medical Center

Odeya David

Soroka Hospital: Soroka Medical Center

Eilon Shany

Soroka Hospital: Soroka Medical Center

Annick Raas-Rothschild

Edmond and Lily Safra Children's Hospital

Yair Anikster

Edmond and Lily Safra Children's Hospital

Katya Kneller

Edmond and Lily Safra Children's Hospital

Eli HersHKovitz

Soroka Hospital: Soroka Medical Center

Yuval E. Landau

Schneider Children's Medical Center of Israel

Ronen Spiegel

Haemek Medical Center: Emek Medical Center

Yoav Zehavi

Haemek Medical Center: Emek Medical Center

O Staretz-Chacham (✉ staretz@bgu.ac.il)

Soroka University Medical Center <https://orcid.org/0000-0001-6975-4909>

Keywords: lysosomal storage disorder, COVID-19, enzyme replacement therapy

Posted Date: April 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-400008/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background- Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) is the causative agent of the current COVID-19 pandemic. Lysosomal storage disorders (LSD) comprise of 70 inherited inborn errors of metabolism. Affected individuals suffer from multi-systemic involvement with variable severity and rate of disease progression between different diseases. Some of the LSDs have established treatments whether parenteral, or oral therapies. The full impact of the COVID-19 pandemic together with the lockdown on the wellbeing and medical management of patients with rare diseases, such as LSDs, is widely unknown. Herein, we describe the effects of the COVID-19 pandemic and its associated mandatory home lockdown on patients with LSDs in Israel.

Results- We present a prospective multi-center questionnaire study including 48 LSD patients from four medical centers in Israel. The study objective was to assess the impact of the COVID-19 pandemic restrictions on individuals with LSDs in Israel, as reported by their caregivers. Secondary objectives were to assess the morbidity from SARS CoV-2 in LSD patients and the impact of changes in mood and behavior on compliance to treatment and to assess the relationship between changes in mood to changes in cognition and behavior. Thirty one of 38 patients (82%) who received any kind of regular treatment did not miss treatments. Among patients receiving enzyme replacement therapy (ERT) in the in-hospital setting, 5 patients (20%) experienced treatment disruptions. Four patients had tested positive for SARS-Cov-2 virus infection by PCR. Seven out of the 48 patients (14%) described mood changes with cognitive and motor deterioration during the home quarantine.

Conclusions- We observed high rates of treatment adherence and low morbidity through the COVID-19 pandemic in patients with LSDs in Israel. LSDs patients can be a model for patients with complex chronic diseases requiring routine treatments and surveillance during a pandemic or other disruption of daily routine.

Background

Lysosomal Storage Disorders (LSD) comprise of 70 inherited inborn errors of metabolism. While individually rare, as a group their incidence is 1:5000 live births¹. The lysosome is responsible in the cells for macromolecule catabolism, recycling and signaling. Mutations in lysosomal genes lead to impaired encoded protein and result in lysosomal malfunction and the gradual accumulation of substrates inside the lysosome¹. Affected individuals suffer from multi-systemic involvement with variability in severity and rate of disease progression among the different diseases. Some of the LSDs have established treatments, whether stem cell transplantation, parenteral, such as enzyme replacement therapy (ERT) or oral treatments, such as substrate reduction therapy or chaperone therapy. Additionally, all affected patients need supportive therapy such as physical therapy, etc. Both ERT and supportive therapy are ambulatory treatments provided either in-hospital, out-patient clinic or at home setting.

In mid-December 2019, a new strain of betacoronavirus emerged as the causative pathogen of pneumonia in the city of Wuhan, Hubei Province, China. The new strain rapidly spread resulting in a worldwide pandemic^{2,3,4}. In February 2020, the World Health Organization (WHO) designated the new virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the ensuing disease as coronavirus disease 2019 (COVID-19)⁵. In March 2020, the WHO labeled it a global pandemic. COVID-19 soon spread across the globe, with more than 100,000,000 patients diagnosed by January 2021.

From March 19th to April 30th and from September 18th to October 14th, the Israeli government declared mandatory home lockdown on all citizens except for emergency cases, due to the local pandemic situation.

Individuals with certain chronic disorders are especially vulnerable to severe effects of SARS-CoV-2 infection with significant morbidity and mortality^{6,7}. We hypothesized that due to the special challenges of individuals living with chronic diseases, the COVID-19 pandemic related restrictions impacted their wellbeing as well as their medical conditions.

The objective of this study was to assess the impact of the COVID-19 pandemic restrictions on individuals with LSDs in Israel, as reported by their caregivers. Secondary objectives were to assess the impact of changes in mood and behavior on compliance to treatment and to assess the relationship between changes in mood to changes in cognition and behavior.

Materials And Methods

Study Design

This was a prospective multi-center questionnaire study conducted between the two lockdowns that started at March-October 2020. The study was approved by the local ethics committee of the correspondent author. Physicians caring for individuals living with LSDs in Israel were reached via e-mail and phone calls and asked to fill a questionnaire. The physicians were approached from a list of known Israeli metabolic physicians. The questionnaires included demographic data such as disease type, age, gender and were also focused on patients' adherence to the different treatment modalities, as well as the effects of the prolonged lockdown on their motor function, mental wellbeing and/or behavior. The physicians filled the questionnaire based on their knowledge of the patients and with the help of their care-givers.

Statistical analysis

All statistical analyses were conducted using SPSS Statistics for Windows, version 25.0 (SPSS Inc., Chicago, USA). For descriptive analysis, central tendency and dispersion values were calculated. For univariable analysis chi square test was used.

List of abbreviations

COVID-19, coronavirus disease 2019; ERT, enzyme replacement therapy; GD, Gaucher disease; LSD, Lysosomal storage disorders; MPS, mucopolysaccharidosis; NCL, neuronal ceroid lipofuscinosis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

Results

Eight out of 15 physicians responded with information on a total of 48 patients treated in four different medical centers in Israel. The patient cohort comprised of 29 males (60%) and 19 females (40%), ages between 1 to 42 years, with 46 of the patients (95%) under 18 years of age (Table 1) and a median age of 6.5 years (range 41). Patients included in the study were affected by the following diseases:

mucopolysaccharidosis (MPS) (n=27; 56%): 1 MPS type I (Hurler syndrome), 2 MPS type II (Hunter syndrome), 8 MPS type IIIA (Sanfilippo A syndrome), 14 MPS type IVA (Morquio syndrome), 2 MPS type VI (Maroteaux-Lamy syndrome); Pompe disease (n=7; 15%), Niemann Pick type C disease (n=6; 12%); Gaucher type 1 disease (n=2; 4%); neuronal ceroid lipofuscinosis (NCL) (n=2; 4%; of these one with NCL5 and another with NCL6); Niemann Pick type A disease (n=1; 2%); cystinosis (n=1; 2%); I cell disease (n=1; 2%); and Lysosomal acid lipase deficiency (n=1; 2%).

Four patients had tested positive for SARS-Cov-2 virus infection by PCR, all four were patients diagnosed with Sanfilippo A and two of them were siblings.

Regarding treatment modalities of underlying LSD, 26 patients (55%) are treated with intravenous ERT, and 15 patients (31%) are on different oral therapies, such as chaperone therapy or supportive, while 7 patients (14%) have no regular therapies.

Regarding ERT treated patients, before the COVID-19 outbreak, 24 patients (92%) were regularly receiving intravenous infusions in the hospital and two patients (8%) were on home-therapy. Due to the pandemic, two additional patients were transferred to home therapy.

Thirty one of 38 patients (82%) who received any kind of regular treatment did not miss treatments. Among patients receiving ERT in the in-hospital setting, 5 patients (20%) experienced treatment disruptions: three missed an intravenous infusion due to their parents' fear of arrival to the hospital, one patient missed an intravenous infusion due to logistic issues in his medical center and one patient missed an intravenous infusion due to low adherence, regardless of the COVID-19 pandemic.

Seven out of the 48 patients (14%) described mood changes with cognitive and motor deterioration during the home quarantine (Table 1).

Table 1: Descriptive analysis from questionnaire data

Questionnaire data	No. (%)
Total	48 (100)
Males (%)	29 (60)
No. (%) of patients treated with ERT or other parenteral	28 (58.3)
No. (%) of patients that missed ERT or parenteral treatments during COVID-19 pandemic	7 (25)
No. (%) of patients that were under the age 18 years during COVID-19 pandemic	46 (95)
No. (%) of patients reporting mood deterioration during COVID-19 pandemic	9 (18.8)
No. (%) of patients reporting increased aggressiveness during COVID-19 pandemic	7 (14.6)
No. (%) of patients reporting cognitive function decline during COVID-19 pandemic	8 (16.7)
No. (%) of patients reporting motor function decline during COVID-19 pandemic	11 (23.9)

ERT- Enzyme Replacement Therapy.

Patients who missed ERT had 7.6 times more mood deteriorations ($P_v=0.09$) than patient who were compliant to therapy. Also, the odds ratio for cognitive function decline was 20% higher in patients who missed ERT compared to patients who were compliant to therapy ($P_v=0.08$). Patients with mood deterioration had 76 times more aggressiveness, 37 times more cognitive function decline and 12.8 times more motor function deterioration (all with $P_v<0.001$) (Table 2).

Table 2: Univariate analysis for symptoms associated with missed ERT or mood deterioration, respectively

Symptom onset	Association with missed enzymatic replacement therapy		Association with mood deterioration	
	Pv	OR (CI)	Pv	OR (CI)
Mood deterioration	0.09	7.6 (0.6-101.8)		
Aggressiveness	1	NA	<0.001	76 (6.7-855.9)
Cognitive function decline	0.08	1.2 (0.9-1.6)	<0.001	37 (5.1-269.7)
Motoric function deterioration	0.3	2.8 (0.3-23)	0.001	12.8 (2.4-68.4)

Discussion

This study on LSD patients showed a relatively significant and undisrupted care during the COVID pandemic in Israel in spite of significant psychological stress of these patients as expressed by

aggressiveness, cognitive function decline and motoric function deterioration that were related to general mood deterioration.

The routine management of patients affected with rare inborn errors of metabolism with multisystemic involvement is complex and carries a significant burden on the patients and their caregivers, all the more so during a global pandemic.

Regular drug supply and deliveries were ensured all over Israel. No interruption or modification occurred for patients receiving oral therapy, except for Amborxol treatment for Gaucher patients due to supply problems.

In our cohort we observed overall high adherence to ERT, even though most of the patients receive treatment in the in-hospital setting and not at home. All patients received therapy in hospitals in which COVID-19 patients were also admitted. In all cases the treatment was in areas well-separated between COVID-19 and non-COVID-19 patients. Sechi et al. described the impact of the COVID-19 related healthcare crisis on treatments for patients with LSDs in Italy⁸. No interruption or modification occurred for patients receiving only oral therapy. Regarding patients on ERT, all patients who were already on home-therapy continued their infusions regularly, while among patients receiving ERT in the hospital nearly half (49%) experienced treatment disruptions, mainly because of parental fear of infection and due to reorganization of the infusion center. The higher rate of ERT adherence in our cohort can be explained by lower mortality rate from COVID-19 in Israel compared to Italy (Johns Hopkins Coronavirus Resource Center) combined with the Israeli healthcare system response to the pandemic which excluded disruptions to chronic treatment including ERT for LSDs patients. An important issue contributing to this result is the secluded areas these ambulatory patients are treated in, which reduced families' fear of getting to the hospital during the pandemic. Of note, our results were comparable with those recently reported in a cohort of Gaucher Disease patients in Spain, in whom dose interruptions in patients treated in in-patient settings were reported in 25% of patients⁹.

As could be expected most of the patients were reported with mood changes and cognitive decline suffer from neurodegenerative diseases, five are affected by Sanfilippo A and one is affected by NCL-6, that have more profound baseline neurological symptoms. The questionnaires in those patients were filled by their treating physicians with the help of their caregivers, who all noted that the prolonged home quarantine may be the reason for the accelerated deterioration of the clinical and mental status of our patients. Although not all patients with LSDs receive regular paramedical treatments, the reasons for missed treatments can be decreased availability of paramedical treatment during the COVID-19 pandemic from medical side, and the parents' perception of those treatments as less significant during the COVID-19 pandemic, from the patients'/families' side. Patients with LSDs may be considered at high risk of developing severe complication in case of SARS-CoV-2 infection, especially, since they tend to have a multisystem involvement. From our survey data, among 48 reported patients, only 4 patients (6.2%) had tested positive for SARS-CoV-2, and all of them had mild disease with no requirement for hospital admission. Compared to the general Israeli population, the infection rate among LSDs patients is

higher (4.4% based on the Israeli Ministry of Health data) but the mortality and morbidity rate is significantly lower. This is actually supported by a study of transcriptomic analyses performed on MPS patients' cell lines by Pierzynowska et al. that showed that MPS patients' cells may have lower susceptibility to infection by SARS-CoV-2 due to specific changes in expression of genes coding for proteins involved in interactions with viral proteins¹⁰. Another important point is the vast majority of the described Israeli cohort includes younger patients which could partially explain the mild disease, as occurs also in the general pediatric population in Israel. Fierro et al. described a cohort of 181 patients with Gaucher disease (GD) and SARS-CoV-2 infection in New York¹¹ and they concluded that GD patients do not appear to have an increased risk for severe SARS-CoV-2 infection. The authors also raise the possibility that lysosomal dysfunction underlying GD pathophysiology, may somehow protect or otherwise modify responses to SARS-CoV-2 infection, and this could also be the reason in other LSD patients, as described here.

Finally, an important and often overlooked aspect of the holistic care of children and adults affected with inborn errors of metabolism, and specifically LSDs, is the psychological state and wellbeing. Recently, Fiumara et al.¹² evaluated the psychological impact of the COVID-19 pandemic on a cohort of 15 LSD patients in Italy. While their results did not reach statistical significance when compared to age-matched controls, an important finding universally shared by all participants was the reportedly increased feelings of anxiety, worry and uncertainty. As the investigators noted, home reclusion further contributed to feelings of being excluded, known all too well to individuals affected by rare chronic disease. While our study was not designed to evaluate specific patient perceptions and feelings, the overall added psychological burden associated with the global pandemic was reflected in the reported mood changes associated with motor and cognitive deterioration during the prolonged home lockdown. These can be compared to the general population as reported by Terry et al that in a cohort of 1062 participants showed results that confirmed significant mood disturbance during the period of COVID-19 restrictions, representing increased risk of psychopathology, more significant in the younger population under 25 years¹³.

Our study limitation is the limited size of the cohort and the lack of controls and we therefore compared to published papers of healthy population around the globe, although a cohort of 50 participants in rare diseases is regarded differently than in other areas. Our results reflect the Israeli organization of the Health System that at the time of the study was not yet faced with massive loads of patients.

Conclusion

We observed high rates of treatment adherence and low morbidity through the COVID-19 pandemic in patients with LSDs in Israel. As this pandemic created a new daily routine in all aspects of life, it is still unclear what will be the cumulative outcomes in COVID-19 infected patients and in uninfected patients with chronic disease for whom treatment was interrupted. LSDs patients can be a model for patients with complex chronic diseases requiring routine treatments and surveillance during a pandemic or other disruption of daily routine.

Declarations

Ethics approval - this study was approved by the ethic committee of Soroka University Medical Center.

Consent for publication- Not applicable.

Availability of data - the datasets used and/or analyzed during the current study are available from the corresponding author for reasonable request.

Conflict of interest - The authors declare that they have no conflict of interest.

Funding - There was no funding.

Authors' contributions –

Eyal Kristal, Guy Hazan, Ben Pode-Shakked and Orna Staretz- Chacham were involved in conception, design, interpretation of data, drafting and revising, and final approval. All authors were involved in acquisition of data, drafting and revising.

Acknowledgements- Not applicable.

References

1. Platt FM, Azzo A, Davidson BL, Neufeld EF. Lysosomal storage diseases. *Nat Rev | Dis Prim*. Published online 2018:1–25. doi:10.1038/s41572-018-0025-4.
2. Zunyou W, Jennifer M. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):25–8.
3. del Rio C, Malani PN. 2019 Novel Coronavirus – Important Information for Clinicians. *JAMA*. 2020;323(11):1039–40. doi:10.1056/NEJMoa2001191.
4. Surveillances V. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) – China, 2020. 2020;2(8):113–122.
5. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020.pdf. Published online 2020:1–5.
6. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr Int J Paediatr*. 2020;109(6):1088–95. doi:10.1111/apa.15270.
7. Dayal D. We urgently need guidelines for managing COVID-19 in children with comorbidities. *Acta Paediatr Int J Paediatr*. 2020;109(7):1497–8. doi:10.1111/apa.15304.
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*. Published online 2020:1–2.

9. Andrade-campos M, Escuder-azuara B, López L, Frutos D. 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 J.* 2020;85(June):1–5.
10. Pierzynowska K, Gaffke L, Węgrzyn G. Transcriptomic analyses suggest that mucopolysaccharidosis patients may be less susceptible to COVID-19. *FEBS Lett.* 2020;594(20):3363–70. doi:10.1002/1873-3468.13908.
11. Fierro L, Nesheiwat N, Naik H, Narayanan P, Mistry PK, Balwani M. Gaucher disease and SARS-CoV-2 infection: Experience from 181 patients in New York. *Mol Genet Metab* Published online. 2020. doi:10.1016/j.ymgme.2020.12.288.
12. 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(9):2716. doi:10.3390/jcm9092716.
13. Terry PC, Parsons-Smith RL, Terry VR. Mood Responses Associated With COVID-19 Restrictions. *Front Psychol.* 2020;11(November):1–10. doi:10.3389/fpsyg.2020.589598.