

## Impact of COVID-19 on the management of patients with Lysosomal Storage Disorders

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**Lysosomal storage disorders (LSDs) are a group of inborn errors of metabolism (IEM) characterized by multisystemic involvement with multi-organ complications. The recent Covid-19 pandemic had a major impact on the management and treatment of patients with LSDs, who also experienced significant psychological distress following the pandemic. Several experiences described so far demonstrate that telemedicine and home therapy programs are valid tools for the follow-up and care of patients suffering from these complex chronic diseases.**

Lysosomal storage disorders (LSDs) are a group of inborn errors of metabolism (IEM) due to the lack of lysosomal enzymes involved in substrate degradation with a consequent multisystem accumulation of toxic material (1). The resulting clinical picture is characterized by a multisystemic involvement with multi-organ complications (2-10), extreme variability of the clinical phenotype even in the context of the same disease due to mechanisms not yet fully understood (11, 12), and a progressive course of clinical manifestations. In the last years, understanding the pathophysiology and molecular mechanisms of these disorders has allowed the identification of a growing number of promising therapeutic approaches, although not all of them yet usable in clinical practice (1, 13, 14). Therefore, the management of LSDs patients requires periodic

visits to monitor the progression of the diseases and allow the early detection of any organ complications. Furthermore, for those LSDs for which specific therapy is available, it is essential that a therapeutic continuity is guaranteed, which, in some cases, requires frequent visits to the hospital, as happens for patients in Enzyme Replacement Therapy (ERT).

The recent pandemic caused by Sars-Cov-2 infection has had an important impact on the health management of all non-Coronavirus Disease-19 (Covid-19)-related diseases, including LSDs, and several experiences of different Clinical Centers involved in follow-up and treatment of these highly complex diseases have been described so far.

### *Impact of COVID-19 on LSDs*

During the early stages of the pandemic, there

*Keywords: Lysosomal storage disorders, enzyme replacement therapy (ERT), COVID-19 pandemic*

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0393-974X (2022)

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was little knowledge on the effects of Sars-Cov-2 infection, and a profound health care reorganization has been necessary to minimize the risk of infection while ensuring continuity of care for patients with complex chronic diseases. Sechi et al. (15) reported their experience with 102 patients affected by different LSDs coming from 16 different Italian Regions during the first wave of the outbreak. At the beginning of the pandemic, 71 patients were receiving ERT and 26 were on oral treatments. There were no problems in medicine supply, and no interruption or modification has been registered for patients in oral therapy. All patients receiving ERT at home continued their ERT infusions regularly, while 49% of LSDs patients receiving ERT in the hospital experienced disruption. These results were in line with other data about the effects of Covid-19 outbreak on rare metabolic diseases, provided by the European Reference Network for Hereditary Metabolic Diseases (MetabERN) by performing two surveys: one directed to patients' organizations, and one directed to healthcare providers, in the period between March and April 2020. Based on the results obtained from the surveys, visits were mostly cancelled or postponed, and most treatments were reduced or suspended (16). Considering that the recommencement of ERT after temporary treatment interruption does not fully reverse clinical decline due to the temporary discontinuation, home therapy seems to be useful to maintain therapeutic continuity for patients with LSDs during the COVID-19 pandemic (17), as had already been shown by experiences prior to the pandemic (18).

Brunetti-Pierri et al. reported the experience of a single Italian centre involved in the care of IMD patients during the COVID-19 outbreak (19). In the first months of a pandemic, it has been necessary to rearrange, reduce, or discontinue standard activities (e.g., outpatient clinics, follow-up evaluations, ERT, and clinical trials) and to convert most follow-up visits into remote visits. Telemedicine also proved to be a useful tool for MetabERN experience (16), allowing patients to be followed despite the pandemic and, at the same time, protecting them from the infection.

Patients with chronic multisystemic disorders, like LSDs, are considered at greater risk to have higher morbidity and mortality consequent to Sars-

Cov-2 infection, and the first paediatric death in Italy was of a 5-year-old girl with mucopolysaccharidosis type II, emphasizing that in children with a severe metabolic disorder COVID-19 may have a worse prognosis (20). The strategies implemented to minimize the risk of infection in these patients allowed no proven infection to be recorded in the experiences described by several authors (15, 19, 21). Nevertheless, Elmonem et al., who collected data from 16 medical centres in Europe, Asia, and Africa specialized in IEM, reporting a median decline of IEM related services in March-May 2020 compared to the same period in 2019 in the range of 60 to 80%, described 2 patients both suffering from Gaucher Disease (GD) that were confirmed with COVID-19 infection and underwent a clinical decompensation (22). A group of investigators and physician experts in GD along with patient advocacy organizations in the United States proposed practice recommendations for the management of Gaucher patients during the SARS-CoV-2 pandemic (23), and Fierro et al. characterized a cohort of 181 GD patients to understand the determinants and the impact of SARS-CoV-2 infection during the peak of the pandemic in the New York City metropolitan area (24). The study results showed that 45 patients reported a primary exposure to someone with COVID-19, and 17 (38%) of these patients reported at least one COVID-19 symptom. Sixteen out of 88 patients tested were positive. No patient required COVID-19-specific treatments, and there were no deaths, suggesting that GD does not seem to be associated with severe outcomes of SARS-CoV-2 infection.

Finally, an aspect not to be underestimated about the effects of the pandemic on patients with LSDs concerns the psychological impact resulting from isolation and fears deriving from a health event of this magnitude. Fiumara et al. (25) evaluated how and to which extent the Sars-Cov-2 outbreak changed LSDs patients' behaviour and feelings. The administration of a phone interview to 15 patients, compared to the same interview administered to an age-matched control group, revealed an increase of anxiety, worries, and uncertainty in all interviewed people, with qualitative differences between the two groups, underlining the vulnerability and isolation of patients with LSDs.

## DISCUSSION

The COVID-19 pandemic has represented a challenge for the healthcare system, particularly for the management and treatment of complex chronic diseases such as LSDs. With the implementation of telemedicine and home therapy programs, the reorganisation of the clinical centres has made it possible to minimize the risk of infection, guaranteeing continuity of care for these patients. Despite the complexity of these diseases, few cases of severe Sars-Cov-2 infection have been reported in patients with LSDs. Nevertheless, the psychological impact of the pandemic is not to be underestimated in the general population and even more in this fragile patient group. The molecular pathophysiology of severe Sars-Cov-2 infection is now more understood and genetic mechanisms implicated in disease initiation, severity and progression are increasingly recognized (26).

## CONCLUSION

Omic-related and similar techniques will be important to further understand Sars-Cov-2 infection, as these technologies have been proven nowadays as essential in dissecting different complex paediatric diseases or mechanisms likely implicated in paediatric health (27-29).

*Conflicts of interest*

The authors declare that they have no conflict of interest.

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