Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Gaucher disease in the COVID-19 pandemic environment: The good, the bad and the unknown

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Early in the course of the novel coronavirus disease 2019 (COVID-19) pandemic, the rare disease community anticipated that patients with lysosomal and other metabolic disorders would be at increased risk for poor disease outcomes and mortality from the SARS-CoV-2 virus.

The pandemic has resulted in a wide range of challenges to the delivery of medical care, the nature of which has varied, depending on a patient's underlying disorder. As the early understanding of the pathophysiology evolved, researchers demonstrated that as part of enhancing its survival and infectivity, the SARS-CoV-2 particles remain infective by exiting cells through a process where lysosomes get de-acidified in coronavirus-infected cells, resulting in a marked disruption of lysosomal enzyme activities [6]. As a result of this discovery, for those treating patients with rare lysosomal disease, predicting the unique clinical complications that may arise related to the SARS-CoV-2 infection is unchartered territory. There were multiple additional causes for heightened concerns, and guidance from rare disorders providers and patient support groups stressed an increased need for surveillance and implementation of precautions to avoid infection, as well as measures to ensure critical ongoing standard of care disease management. However, with the sparse availability of early pandemic outcome data, it has been difficult to provide informed guidance regarding the specific risk of infectivity and disease sequelae for patients with specific lysosomal disorders. Focusing on the prototypic lysosomal disorder Gaucher disease, investigators were initially concerned that with SARS-CoV-2 infection, both the lysosomal involvement and the accompanying cytokine storm or dysregulation of inflammatory cytokines might augment Gaucher disease pathophysiology, resulting in increased mortality in infected patients.

During the early phase of the pandemic, a group of Gaucher investigators together identified potential Sars-CoV-2-related management challenges specifically for the Gaucher patient population, providing some suggestions and identifying concerns requiring additional research [7]. These included the need for epidemiological studies, studies regarding the response of patients with Gaucher disease to Sars-CoV-2 and/or its pharmacological interventions and investigations into the impact of Sars-CoV-2 disease on the Gaucher patient community. Moreover, they addressed the challenges to maintaining ongoing requirements for health-sustaining medical treatments for lysosomal diseases, such as regular infusions of costly intravenous enzyme preparations that require access to providers and specialized clinics. There was also at least a theoretical concern that patients with Gaucher disease might be especially at risk if early Sars-CoV-2 treatments like hydroxychloroquine, that could disrupt autophagy needed to maintain homeostasis, were administered. In response to this call to action, both patient groups and physician investigators have attempted to educate and to survey the Gaucher patient population to assess the evolving impact of the Sars-CoV-2 disease and pandemic on their care and health [3,5,9,10]).

Emerging clinical reports like the study by Fierro *et al* provide some preliminary reassurance for the Gaucher patient population [4]. Focusing on patients exposed to the virus in the early New York City epicenter, the authors conducted a cross-sectional study in a cohort of 181 patients with Gaucher disease that included 150 adults and 31 children. Among this Gaucher cohort, 71% were chronically being treated with either enzyme replacement or substrate inhibitor therapy. Approximately one third of the adults reported being exposed to SARS-CoV-2, although the majority of these respondents did not develop symptoms. Of 94 patients tested by serology, 18 had positive results. Comorbidities, *GBA1* genotype and the type of Gaucher disease therapy did not correlate with the probability of being symptomatic or testing positive.

Major confounding variables affecting the interpretation of this study are related to the rapid evolution of the pandemic and our understanding of SARS-CoV-2. Much of the data in this Gaucher study were collected early in the pandemic and did not include state-of-the-art quantitative testing or diagnostic confirmation. Instead, out of necessity in light of the period when the data was collected, the authors had to rely on a symptom scoring system based on patient reporting. Only 18 of the 181 patients surveyed reported having experienced three or more related symptoms. Fourteen of the 18 had clinical diagnostic testing, with 10 having SARS-CoV-2 positive results, making it more difficult to ascertain the true incidence of infection in this cohort. The Gaucher patient cohort studied was not particularly diverse, being mostly of Ashkenazi Jewish ancestry (85%), although it did include three patients with type 3 Gaucher disease and 11 patients who had undergone splenectomy. However, despite these limitations, it was reassuring that none of the SARS-CoV-2 infected patients with Gaucher disease in this

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series required Sars-CoV-2- specific treatments or hospitalization, and significantly, that there were no mortalities. As the SARS-CoV-2 pandemic has evolved, additional reassurance against a high rate of infectivity or incidence of Sars-CoV-2-related complications in Gaucher or lysosomal disease patient cohorts has begun to emerge from reports of Sars-CoV-02 cases in patients with lysosomal storage disorders in Europe, [1], Israel [11] and Morocco [8]. The series from Spain [1] did describe one SARS-CoV-2 -related death in a 79-year-old patient with Gaucher disease who had various comorbidities including diabetes. As in the general population, it is logical that older age and other comorbidities are also negative prognostic factors for those with Gaucher disease.

It is anticipated that there will be many subsequent reports assessing the impact of the pandemic on specific populations of patients with rare disorders. Now that more quantitative testing and antibody assessment is more accessible, it should be easier to characterize such cohorts with increased precision and by more rigorous standardized clinical research criteria. Such criteria should encompass at least three aspects of disease acquisition and surveillance, including the type and route of clinical diagnostic determination of disease, as well as the presence or absence of Sars-CoV-2 antibodies, the detailed timeline and course of disease, and the impact on the underlying disorder. In order to facilitate comparisons to other cohorts, it is critical that descriptions of the disease course include an accurate timeline of the disease progression, the range of associated symptoms, and disease parameters reflecting the severity of infection. Reports of the impact of Sars-CoV-2 on the patients' underlying disease should include relevant tracked biomarkers and other associated laboratory values, as well as assessments regarding potential exacerbation of underlying conditions or comorbidities. Rigorous longitudinal studies might also uncover unanticipated long-term disease sequelae. Such data may better guide treating providers in establishing consensus management guidelines for the remainder of this or future pandemics.

Another fascinating aspect mandating additional investigation is whether the relatively low incidence and relatively benign course of Sars-CoV-2-related complications in patients with Gaucher disease may be opening a window into an unanticipated phenomenon, protective of Sars-CoV-2 infection and/or its complications. There has been preliminary speculation, based on the low number of cases of Sars-CoV-2 among patients with Gaucher disease in Israel and Australia, that the accumulated glycosphingolipids in patients with Gaucher disease might promote immune tolerance rather than enhancing inflammation as a result of exposure to the virus [11]. Similar to what has been hypothesized in Nieman Pick type C, it is possible that the inherent Gaucher disease and abnormal lysosomal environments in general may be an “unfavorable” milieu for SAR-CoV-2 infectivity [2]. Additional carefully collected epidemiological data may help to determine whether the infectivity and disease manifestations in patients with Gaucher disease or other lysosomal storage disorders differs from the general population. If this indeed is true, further study of the factors underlying this observation could lead to novel and improved therapeutic avenues for patients infected with Sars-CoV-2.

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