Commentary

Gaucher disease and SARS-CoV-2 infection: Emerging management challenges


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1. Introduction

In the late winter of 2019, emergence of the SARS-CoV-2 virus led to the COVID-19 pandemic, manifesting in a serious illness affecting over a million people around the world, including the United States, during the spring of 2020 [1]. During this pandemic, people with preexisting medical conditions are at higher risk of severe, potentially life-threatening effects of SARS-CoV-2 infection [2]. Not only is there the likelihood of increased morbidity and mortality if these individuals become infected with the virus, but the social and economic consequences of COVID-19 may significantly impact their access to critical healthcare resources. Among individuals with rare diseases, the implications of the pandemic may be unique, and can present specific management challenges. Moreover, the pandemic provides an unprecedented opportunity to research aspects related to immunity, lysosomal dysfunction and disease pathogenesis in distinct rare disease
communities which will ultimately enhance clinical care. A group of investigators and physician experts in Gaucher disease along with patient advocacy organizations in the United States convened to propose management guidelines and to identify research questions during these challenging times. The overarching goal of this collaborative group is to delineate the emerging impact of the SARS-CoV-2 pandemic on patients with Gaucher disease and to develop optimal clinical practice guidelines for managing the infection.

Gaucher disease (GD) is caused by recessively inherited homozygous or biallelic pathogenic variants in GBA1, the gene encoding the lysosomal enzyme, glucocerebrosidase (GCase, acid β-glucosidase, EC 3.2.1.45). These variants lead to varying degrees of deficient and/or defective glucocerebrosidase function, and the lysosomal accumulation of excess glucosylceramide (glucocerebroside, Gb1), glucosylsphingosine (lyso-Gb1), and other sphingolipids [3,4]. GD is among the most common lysosomal diseases affecting approximately 1 in 40,000 individuals. However, in the Ashkenazi Jewish population, the frequency is much higher, affecting as many as 1 in 250 individuals. The disease is characterized by vast phenotypic heterogeneity and is classically divided into non-neuropathic (type 1, GD1) and neuropathic types (GD2 and GD3). These variants share the common feature of major systemic macrophage involvement, manifesting with varying degrees of hepatosplenomegaly, cytopenia and bone disease. There is accumulation of glycosphingolipid-laden macrophages (“Gaucher cells”) in the spleen, liver, lymphoid and hematopoietic tissues, and somewhat infrequently, in the lung or kidney [4,5]. A subset of patients, especially those that have undergone prior splenectomy for hypersplenism, develop pulmonary vascular disease manifesting as pulmonary hypertension or hepatopulmonary syndrome. Additionally, in GD1 there are age-related phenotypes in a small subset of patients that can include gammopathy/myeloma, other hematological malignancies and certain solid organ malignancies [6]. The neuropathic forms have a spectrum of brain involvement, ranging from a rapidly progressive lethal neurodegenerative disorder of infancy (GD2) to more indolent and variable CNS involvement with eye movement abnormalities (gaze palsy), a hallmark neurological manifestation (GD3) [7]. A subset of patients with GD, as well as their heterozygous carrier relatives, have an increased life-time risk of developing Parkinson’s disease, although the complete mechanism underlying this association is not fully delineated [8]. The degree of clinical heterogeneity in GD is remarkable, and can be viewed as a continuum of phenotypes [9]. In general, prior to treatment patients with GD have impaired macrophage function and immune dysregulation involving multiple myeloid cell lineages leading to chronic metabolic inflammation [10-14]. Additionally, some patients had splenectomies performed before the advent of therapy, and others harbor immunological abnormalities [15]. Together, these factors could portend poor outcomes when patients with GD encounter infectious disease.

Effective treatments for Gaucher disease are available that successfully reverse many of the systemic non-neurological manifestations of the disease. Administration of the two therapies, enzyme replacement therapy (ERT) [16] and therapy preventing substrate accumulation (SRT) (for GD1) [17] are widely used. Each has specific considerations that may be impacted by aspects of the COVID-19 pandemic.

2. Are patients with Gaucher disease at increased risk of COVID-19 infection relative to the general population?

In the general population, SARS-CoV-2 has a higher infectious risk and mortality compared to seasonal influenza [18]. Older adults and people of all ages who have serious underlying medical conditions are at higher risk for severe illness from COVID-19 [19]. Specific risk factors for poor outcome from SARS-CoV-2 include male sex, diabetes mellitus types 1 and 2, obesity, pre-existing heart disease, kidney disease, hypertension, immunodeficiency and chronic lung disease. Three stages of SARS-CoV-2 disease are recognized, which is important to keep in mind when managing patients with GD infected with the virus. In stage 1 [20], inhalation of viral particles is followed by ACE2 receptor-mediated uptake and endolysosomal processing of the virus by target cells in the lungs [21]. Early symptoms include fatigue, cough and fevers. The majority of patients (~80%) recover from the infection at this stage, and treatment is only symptomatic. Some 15% of patients progress to silent or overt pulmonary disease (without or with hypoxemia, respectively) and inflammation that appears to prominently involve the interaction of infected cells with macrophages and other myeloid cells (stage 2) [22]. On chest X-ray or CT scan, diffuse infiltrates or ground glass opacities are seen. In managing SARS-CoV-2 infected patients with GD, the top priority should be to identify this stage of the disease, ideally before onset of hypoxemia, as appropriate management can often avert the progression to stage 3, systemic hyperinflammation, multiorgan involvement and acute respiratory disease syndrome (ARDS) requiring ventilatory support. This severe stage 3 disease occurs in ~5% of diagnosed patients and it carries the highest mortality. Inflammation in COVID-19 infection results in a decrease of helper, suppressor and regulatory T cells and of gamma interferon. Comcomitantly, inflammatory cytokines and biomarkers such as interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-α, tumor necrosis factor-α, C reactive protein, ferritin, and D-dimer are elevated in patients with more severe disease. In this most severe stage, patients develop multiorgan failure and thromboembolic events, during which markers of hemophagocytic lymphohistiocytosis (hyperferritinemia, soluble IL2 receptor, etc.) and of myocarditis may emerge [23,24].

Whether patients with GD have a higher risk of infection is an important question. Currently, there are insufficient data to accurately answer this question. Thus, throughout the pandemic, it is imperative to collect epidemiologic data regarding exposures and confirmed infection rates to better inform optimal management and assess potential risks to this population. Prospective banking of patient samples will permit investigators to explore the relevant mechanisms of SARS-CoV-2 infection and pathogenesis specific to patients with GD, delineate overlapping disease pathways if present and identify informative biomarkers.

There are ample scientific reasons suggesting that individuals with GD may be at increased risk of infection and/or complications of SARS-CoV-2. Both GD and the novel coronavirus appear to be characterized by lysosomal involvement or disruption, and both share the central role of proinflammatory responses to a causal insult. In GD, the accumulation of inflammatory and immunoreactive sphingolipids and the resultant lysosomal dysfunction trigger autoinflammatory cascades involving a wide spectrum of myeloid cells, cytokine/chemokine secretion and NLRP3 inflammasome activation [25]. Indeed, elevated cytokines found in SARS-CoV-2 (IL-2R, IL-6, IL-10, MIP1-α and TNF-α), are reminiscent of the pattern described in GD [15,24,26]. Generally macrophages are not considered to be direct targets of the SARS-CoV-2 virus. However, preliminary evidence from human autopsy material shows that ACE2-expressing CD68+ CD169 + macrophages in the spleen and lymph nodes, are positive for SARS-CoV-2 nucleoprotein antigen, suggesting that CD169 + macrophages may directly contribute to viral spread and inflammation in SARS-CoV-2 infection [27]. Moreover, the immunopathology of lung injury in ARDS, the most advanced form of SARS-CoV-2 infection, involves a central role for myeloid cells. Clearly, further investigations are indicated to determine whether SARS-CoV-2 shares disease pathways with GD beyond similarities in the pattern of hypercytokinemia [28-30].

There are also some further considerations. Prior to the advent of current therapies, many patients were treated by splenectomy, and a significant proportion of the older US patients with GD are asplenic [31]. Baseline studies in patients with GD have demonstrated abnormal immunoglobulin levels, some with monoclonal gammopathy, and immune phenotyping has suggested other impairments [32-34]. Rare
patients with pulmonary alveolar and interstitial infiltration or pulmonary hypertension may specifically be at risk [35]. Historically, the role of infections in accentuating the natural history of GD has been proposed. For example, infection with Epstein-Barr virus (EBV), a B cell lymphotropic virus is recognized to result in acute worsening of GD [36]. In splenectomized patients with GD, bacterial infection by encapsulated organisms pose a particular hazard and can be lethal [37]. Yet, there is no report of seasonal influenza resulting in worse outcomes in patients with GD. Anecdotal communications from colleagues in Europe indicate a paucity of SARS-CoV-2 infections among patients followed in their Gaucher clinics. While accurate data is not yet available, this may suggest that vulnerability to the infection is not universal, and that there is heterogeneity in response among patients, similar to that seen in the general population. Alternately, the population with GD may be more familiar with routine hygiene and other measures to protect themselves from infection.

Gaucher disease has always been characterized as a disorder with a widely diverse range of phenotypes and where a significant proportion of patients never reach medical attention or require treatment [38]. The variability in effects of COVID-19 infection rates coupled with the variability in baseline GD disease burden will likely complicate addressing the extent of the vulnerability to infection in this population. However, until this question is appropriately addressed by epidemiological and immunological studies, it is prudent to consider patients at greater than average risk. We recommend strict adherence to guidelines circulated by the Centers for Disease Control (https://www.cdc.gov/coronavirus/2019) regarding hygiene, social distancing and other measures such as personal protective equipment.

3. Management issues for patients with GD infected with SARS-CoV-2

While we are still learning about the infectivity and the disease phenotype of SARS-CoV-2 infection in patients with GD, there are several recommendations that we feel are prudent. These are definitely subject to change as the pandemic evolves and we learn more.

a) Communication: The most important recommendation for patients with exposure to SARS-CoV-2 infection is to maintain close communication with a specialist that is familiar with GD in addition to their primary care physician. A major fear is that at a time of overuse of medical facilities, acute care providers will not be familiar with critical aspects of GD, interfering with optimal care. We recommend that patients carry a letter from their physician describing their diagnosis and special management issues should they need urgent care at a hospital or emergency room. A copy of the most recent Gaucher evaluation would also be helpful for the emergency room physicians.

b) Early testing, monitoring and proactive management of SARS-CoV-2 infection in GD is imperative: Physicians managing SARS-CoV-2 infections in patients with GD should be aware that most treated or mild patients today have a normal life expectancy [39], and that the diagnosis of GD should not be considered a reason to deny maximal intervention, regardless of age. Furthermore, at baseline, patients with GD can have abnormal laboratory findings such as low hemoglobin levels and low platelet counts, elevated ferritin levels, abnormal liver function tests (LFT) or coagulopathy [3,4] and these parameters should not be used in isolation to drive management decisions regarding whether to intervene. It is prudent clinical practice to adopt a preemptive approach to screen and diagnose SARS-CoV-2 in patients with GD based on exposure history and/or early disease symptoms. Early diagnosis of SARS-CoV-2 infection underpins optimal management and timely disease intervention. When it becomes available, anti-viral antibody testing is also recommended. Initial symptoms of COVID-19 include fever, malaise, cough, impairment of sense of smell and/or taste and gastrointestinal disturbance. We believe it is of highest priority to identify patients in early stage 2 disease, i.e., when there is onset of viral pneumonia but before hypoxemia occurs. Stage 2 disease can rapidly progress to advanced disease even in the setting of normal oxygen saturation. Normal home oximetry without overt dyspnea can generate a false sense of stability while pneumonia is progressing silently. However, it is often not feasible in the current environment to obtain chest imaging and it is preferable to avoid sending the patient to an ER. An alternative approach is to obtain laboratory studies including ferritin, D-reactive protein, sedimentation rate, blood counts, liver function tests, and D-dimers. Since some of these values may already be elevated in patients with GD, it is important to compare them to results at baseline. If these are newly elevated, a higher level of care is indicated. The overarching goal should be to prevent the progression to advanced stages of SARS-CoV-2 disease, and to avoid hyperinflammation and multiorgan dysfunction by early and aggressive management of hypoxia. “Prophylactic” use of hydroxychloroquine, with or without azithromycin is strongly discouraged for patients with GD during this pandemic.

c) Management of GD-specific therapies: Enzyme replacement therapy (ERT), regular intravenous administration of recombinantly produced GCase, has been transformative in GD1 and GD3 by greatly diminishing most systemic manifestations and much of the cytokine/chemokine excess. Similar therapeutic effects are obtained by oral substrate reduction therapy (SRT) using inhibitors of glucosylceramide synthase [40]. Monitoring of selected cytokine/chemokines have been explored as “biomarkers” for effectiveness and progress of ERT [41,42]. Chitotriosidase, a marker of alternatively activated macrophages and lyso-Gb1, the accumulating bioactive lipid, are important biomarkers of GD severity and response to therapy [43]. The central concept in successful management of GD with ERT is individualized therapy and meeting therapeutic goals. Hence, close communication with a GD specialist is essential in managing SARS-CoV-2 infection to assess individual risk and continuation of ERT or SRT therapy.

i. Enzyme replacement therapy: Even with infection, it is recommended that ERT be continued without prolonged interruption. Missing one or two infusions will likely not be harmful for some patients, but prolonged interruption could provide the milieu for hyperinflammation and potentially further exacerbate the severity of SARS-CoV-2 infection.

ii. Substrate reduction therapy: Patients receiving the oral SRT, eliglustat require careful assessment of their current GD status, the severity of the SARS-CoV-2 infection and the degree of organ involvement in consultation with a GD specialist. Important considerations are drug-drug interactions with current empirical therapies for SARS-CoV-2 infection, including hydroxychloroquine, antibiotics (such as azithromycin) and antiviral agents. [40,44–48] Other potential complications include reports of hepatic impairment and myocarditis in some SARS-CoV-2 patients [49]. At supra-therapeutic doses, eliglustat has been shown to prolong QTc intervals, which is also a problem with hydroxychloroquine and azithromycin [50]. These considerations underscore the important role of the pharmacologist in multidisciplinary teams managing patients with GD with SARS-CoV-2 infection regardless of comorbidities. Metabolism of eliglustat, like many drugs, is predominantly via the CYP2D6 with minor contribution of CYP3A4 [51], hence assessment of drug-drug interaction with concurrent medications should be performed as the standard clinical practice. With these risks in mind, it may be prudent to interrupt eliglustat treatment when specific therapies for SARS-CoV-2 infection are initiated.

d) Importance of Gaucher comorbidities: A small sub-set of patients with GD may have Gaucher-related comorbidities such as multiple
myeloma and other hematological malignancies, as well as Parkinson’s disease [6]. These are critical age-related comorbidities, as older age itself is clearly associated with more severe outcomes from SARS-CoV-2 infection. In the general population, hypertension, immunodeficiency, chronic lung disease, obesity, diabetes and other chronic disorders have been associated with poor outcome from SARS-CoV-2 infection [52–54]. Patients with GD may also harbor these concurrent chronic disorders and they should be considered in individual risk stratification.

e) Monitor patients with type 3 GD carefully: Patients with GD3 may be especially vulnerable to severe effects of SARS-CoV-2 infection. This is an important group of patients, as they may represent the greatest numbers of patients with GD globally. Patients with GD3 can have severe systemic disease, often with advanced fibrotic complications, parenchymal lung disease, massive intra-abdominal lymphadenopathy with secondary GI manifestations and spinal deformities [55,56]. The pulmonary involvement prevalent in this group may worsen with COVID-19 disease. With increasing availability of PCR and antibody testing for SARS-CoV-2 virus, a strong case can be made for preemptive screening of these patients and family members. A distinct phenotype of GD3 associated with homozygosity for the D409H (p.D443H) mutation in GBA1 may present unique challenges in management since this subtype manifests with cardiac involvement with valvar calcification, aortic calcification and non-atherosclerotic coronary artery disease [57,58].

f) Hyperinflammatory responses: A priori, an inborn error of metabolism characterized by marked chronic metabolic inflammation and accumulation of bioactive lipids, could fuel the explosive hyperinflammation seen in the sickest SARS-CoV-2 infected patients. This “inflammatory storm”, observed in very ill patients with COVID-19, results from excessive and prolonged activation of proinflammatory stimuli. [23,59] The exact mechanisms leading to this potentially lethal manifestation of SARS-CoV-2 infection are not known in detail. However, CD14+CD16+ monocytes and CD4+T lymphocytes are directly involved, as is p38 MAPK activation and the resulting release of proinflammatory agents IL-6 and GM-CSF [30]. It will be essential to prospectively collect US data on whether such hyperinflammation occurs in patients with GD, along with the potential mechanisms involved, in order to enhance clinical care.

g) Pediatric concerns: Recently, SARS-CoV-2 has been reported as possibly linked with a pediatric multi-system inflammatory syndrome disease that has features overlapping with Kawasaki Disease and Toxic Shock Syndrome [60]. This inflammatory syndrome may occur days to weeks after acute COVID-19 illness, with some patients developing cardiogenic or vasogenic shock requiring intensive care for multiple organ dysfunction. Early recognition and prompt referral to in-patient critical care and other specialists is essential.

4. Managing Gaucher disease during the pandemic

Different aspects of the pandemic are impacting the care of patients with GD and the accessibility to aspects of their management. We are still in the process of assessing the healthcare resource gaps of the GD community during the COVID19 pandemic.

a) Enzyme replacement therapy: A large proportion of patients with GD in the United States currently receive ERT, infusions of recombinant glucocerebrosidase available from three different companies, usually administered intravenously at twice monthly intervals. Patients receive ERT at infusion facilities at various clinics or in hospitals, at home, administered by visiting nurses, or by patient self-administration at home. Insurance considerations often dictate how infusions are done. The COVID-19 pandemic has introduced new risk/benefit issues into the equation. Many patients are appropriately avoiding hospitals and clinics where they may be exposed to patients with COVID-19. In the current environment, patients are understandably anxious about allowing home infusions or going to infusion centers, lest they become exposed to a healthcare worker who is an asymptomatic carrier of SARS-CoV-2. Individual discussions with the treating physician regarding the status of the patient’s GD, as well as the logistics of receiving ERT is essential. Some infusion centers and home infusion companies have rapidly adapted to these changed circumstances to continue uninterrupted ERT, but this continues to be a challenge. The availability of home infusion nurses may also be compromised due to nursing shortages, as well as prioritization of availability of personal protective equipment for hospitals overwhelmed with SARS-CoV-2 patients, depending on geographical locations.

Until we understand more about the rate of progression and mechanism of SARS-CoV-2 infection in patients with GD, the general recommendation is not to stop infusions. However, under certain circumstances this may be unavoidable. It is imperative that the decision to alter or halt therapy be made with the input of a GD specialist. In patients who are extremely stable under chronic therapy, it is possible that drug interruptions of weeks to months could be tolerated, as happened during a several month drug shortage a decade ago [61,62]. However, these previously studied treatment gaps did not occur in the context of a severe pandemic. A preferable option to discontinuation of ERT may be to extend the interval of drug infusions, as there is also some evidence that infusions of higher doses given at three- or four-week intervals are effective under certain circumstances [63]. Monitoring the disease before and after any adjustments to the normal administration regimen will be essential, and may help to inform future management. It is recommended that newly started symptomatic patients, unstable patients and those with type 3 GD make every effort to continue their therapy. Those with unavoidable interruptions in therapy should be followed at closer periodic intervals than usual to assess potential worsening of their GD status.

b) Substrate reduction therapy: Since this is an orally administered therapy, the above COVID-19 related interruptions are less relevant. However, drug interactions are important as discussed above, and may necessitate interruption of SRT therapy.

c) Patients in clinical trials: All patients enrolled in a clinical trial should be in touch with the Principal Investigator or their team before making any changes in their treatments, as well as when discussing empirical treatments for SARS-CoV-2 infection.

5. Future prospects: research on COVID-19 and Gaucher disease

This unprecedented experience does provide important new research avenues to explore. Some of these topics are specific to GD, while others may be generalizable to patients with other rare inborn errors of metabolism. The findings observed can help providers to better serve the community during the pandemic and may help to improve future preparedness. This research may also reveal insights into immune and inflammatory pathways relevant to GD pathogenesis.

a) Epidemiological studies: There are multiple lines of inquiry that should be pursued to address questions like the following:

• Is the frequency of infection among patients with GD different than that seen in the general population?
• Is there a correlation with age, sex, ethnicity, body mass index, blood type or therapy status?
• Does the GBA1 genotype or a specific GD phenotype impact the activity and progression of co-existing SARS-CoV-2 infection?
• What is the pattern and natural history of SARS-CoV-2 infection in GD patients? What is the prevalence of asymptomatic and/or mildly symptomatic COVID-19 positive individuals among patients with mild and more severe manifestation of GD? Do different disease
manifestation or comorbidities impact infection rate and/or natural history? Are there specific indicators of prognosis?  
• Because SARS-CoV-2 takes advantage of the lysosomal/endosomal system to infect cells, would genetic variants of genes encoding lysosomal resident-proteins including GBA1 impact SARS-CoV-2 infection course and manifestations?

b) The impact of the pandemic on the patient community: Given the significant socioeconomic and psychological implications of the current pandemic, we propose to survey this patient population with an already existing chronic and rare disorder to assess how they perceive their disease has impacted their medical care during the pandemic, as well as their emotional and psychological health. This will help us to better understand what healthcare resource gaps this rare disease community have identified during the COVID-19 pandemic and how these challenges impact the delivery of optimal health care to these and similarly affected patients. It will also be important to evaluate whether any therapy changes or gaps that occurred during this pandemic impacted their disease.

c) The response of patients with Gaucher disease to COVID-19 and/or its pharmacological interventions: The prospective collection of clinical samples together with clinical data will enable us to determine the response to the infection (symptomatic and asymptomatic) in patients with GD. This will entail collecting samples and data from patients with and without known infection and testing for viral disease together with assessments of inflammation and immune status. Of potential concern is the use of hydroxychloroquine, as this drug is trapped in lysosomal compartments and disrupts lysosomal function [64]. Therefore, patients with an already pre-existing or inborn lysosomal dysfunction may have an increased risk of adverse effects of the drug. For this reason, we would generally try to avoid treatment with hydroxychloroquine, and strongly discourage the “prophylactic” use of this drug.

6. Conclusions

The 2020 SARS-CoV-2 pandemic has introduced many unanticipated challenges related to the treatment and support of patients with rare disease. Like with GD, other inborn errors of metabolism likely have unique aspects that must be considered during these uncertain times. Prospective plans for patient management and for collecting and communicating disease parameters real-time are essential for providing optimal care during the current pandemic and potentially in the future.

References
[10] E. Aflaki, et al., Macrophage models of Gaucher disease for evaluating disease parameters real-time are essential for providing optimal care during the current pandemic and potentially in the future.


[51] L. Becquemont, Type 1 Gaucher disease (CYP2D6-eliglustat), Therapie 72 (2) (2017) 323–326.


