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Gaucher disease and SARS-CoV-2 infection: Experience from 181 patients in New York

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ABSTRACT

SARS-CoV-2 infection carries high morbidity and mortality in individuals with chronic disorders. Its impact in rare disease populations such as Gaucher disease (GD) is unknown. In GD, decreased acid β-glucosidase activity leads to the accumulation of inflammatory glycosphingolipids and chronic myeloid cell immune activation which a priori could predispose to the most severe effects of SARS-CoV-2. To evaluate the determinants of SARS-CoV-2 infection in GD, we conducted a cross-sectional study in a large cohort. 181 patients were enrolled, including 150 adults and 31 children, with a majority of patients on treatment (78%). Information on COVID-19 exposure, symptoms, and SARS-CoV-2 nucleic acid and/or antibody testing was obtained during the peak of the pandemic in the New York City metropolitan area. Forty-five adults reported a primary exposure to someone with COVID-19 and 17 (38%) of these patients reported at least one COVID-19 symptom. A subset of adults was tested (n = 88) and in this group 18% (16/88) were positive. Patients testing positive for SARS-CoV-2 had significantly more symptoms (4.4 vs 0.3, p < 0.001) than patients testing negative. Among patients who were antibody-positive, quantitative titters indicated moderate to high antibody response. In GD adults, male gender, older age, increased BMI, comorbidities, GBA genotype, prior splenectomy and treatment status were not associated with the probability of reporting symptoms or testing positive. No patient required COVID-19-specific treatments and there were no deaths. Our data suggests that GD does not confer a heightened risk for severe effects of SARS-CoV-2 infection feared based on the known chronic inflammatory state in these patients.

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1. Introduction

Individuals with certain chronic disorders are especially vulnerable to severe effects of SARS-CoV-2 infection with significant morbidity and mortality [1,2]. The impact of the COVID-19 pandemic on patients with rare diseases, such as Gaucher disease (GD) is unknown [3]. In GD, an autosomal recessive lysosomal storage disorder [4,5], deficiency of the enzyme acid β-glucosidase leads to the accumulation of inflammatory glycosphingolipids, glucocerebroside and glucosylsphingosine [6]. The complex, multisystem phenotype of GD is caused by chronic metabolic inflammation involving myeloid cells triggered from glycosphingolipid-laden macrophages [7–9]. The pattern of hypercytokinemia and inflammation in GD is reminiscent of that described in SARS-CoV-2 infection [10,11] and therefore, a priori, these patients may be at increased risk of severe disease. Moreover, it is not known whether treatment of GD (enzyme replacement therapy (ERT) or substrate reduction therapy (SRT)) [12–14] is a determinant of the outcome of SARS-CoV-2 infection [3]. A significant number of patients underwent splenectomy prior to the advent of these specific therapies which may add to the risk of severe outcomes from SARS-CoV-2 infection [3], due to defects in cellular immune function and additional comorbidities [15]. Here, we characterize a large cohort of GD patients to understand the determinants and the impact of SARS-CoV-2 infection.

2. Materials and methods

Patients with a confirmed diagnosis of GD were recruited between June and August 2020 at the Lysosomal Storage Disease Program at the Icahn School of Medicine at Mount Sinai (ISMMS) in New York City. The study was approved by the ISMMS Program for the Protection of Human Subjects, and informed consent was obtained from patients or their legal guardians. A survey assessing SARS-CoV-2 exposure, COVID-19 symptoms, and testing over the prior 3 months was developed by the study team and administered in-person, online (REDCap), or via telephone. Medical records for study subjects were reviewed for GBA genotype, treatment history, prior splenectomy, and results of SARS-CoV-2 antibody testing when available. Self-reported testing for SARS-CoV-2 was recorded alongside test results from the medical
chart for those who were tested multiple times. Data was entered into a REDCap electronic database hosted at ISMMS [16,17]. Participant characteristics were described using means and frequencies, and associations were explored using Chi-square, t-tests, and logistic regression, as appropriate. Due to the nonspecific nature of the COVID-19 symptoms, a threshold of 3 or more was used for statistical analyses. All analyses were considered exploratory and conducted in SAS (SAS Institute Inc., Cary, NC) at the 0.05 significance level.

3. Results

Of the 197 patients invited, 181 (92%) completed our survey including 150 adults (mean age 50 years) and 31 children (mean age 9 years). The majority were male (54%), and all had Type 1 GD, with the exception of 3 patients with Type 3 GD [18]. Eighty-five percent of our cohort reported Ashkenazi Jewish ancestry and 61% were homozygous for the common p.N409S (N370S) GBA mutation [19] (Tables 1 and 2). A majority of the adults (117, 78%) were receiving GD treatment with either ERT or SRT. Twenty five percent (45/181) of patients reported having at least one symptom of COVID-19 and 10% (18/181) reported three or more symptoms (Table 3). Symptomatic adults most commonly reported having cough (16, 46%), fatigue (16, 46%), and fevers (15, 43%). Ten pediatric patients were reported to have at least one symptom of COVID-19 with fever being the most common (8, 26%). Of the 14 adults with 3 or more symptoms who reported receiving a test, 10 (71%) reported a positive result.

Forty-five adults (30%) reported a primary exposure to someone with COVID-19 and 17 (38%) of them experienced at least one COVID-19 symptom, with the mean number of symptoms being 3.8. Twenty-eight (62%) adults reporting primary exposure reported no symptoms and 70% (23/33) of adults with exposure who reported testing were negative for SARS-CoV-2. A subset of adults was tested by serology and/or nucleic acid testing (NAT, also referred to as ‘RT-PCR test’) (181) and in this group 18% (16/88) were positive. Patients testing positive for SARS-CoV-2 had significantly more symptoms (4.4 vs 0.3, p < 0.001) than patients testing negative (Fig. 1). Of the 6 children tested by either NAT or serology, two were positive. Fifty-one adult patients with no symptoms reported being tested, and 1 (2%) was positive for SARS-CoV-2 antibodies. One asymptomatic pediatric patient was also found to have SARS-CoV-2 antibodies. In 8 adult and 1 pediatric patients who were antibody-positive, quantitative antibody titers indicated moderate to high antibody response (titers 320 to 2880) [20]. Eleven adults had a prior splenectomy; in this group only one patient reported increased fatigue and was subsequently found to have SARS-CoV-2 antibodies. Three additional asplenic patients reported primary exposure to someone with COVID-19 but had no symptoms or positive test results.

Among 45 patients older than 60, only 7 (16%) reported symptoms and 4 (13%) of those tested were positive. No patient reported hospitalizations, emergency department, or urgent care visits. Patients did not require COVID-19-specific treatments [2,21] and all were managed at home with over the counter medications to control symptoms. There were no deaths from COVID-19 in our cohort. We used logistic regression analysis to assess predictors for SARS-CoV-2 infection among adult patients in our cohort. Male gender, age, increased BMI, or number of comorbidities (including hypertension, diabetes, and heart disease) were not associated with an increased likelihood of testing positive. Among all symptoms reported by adults who reported being tested, feeling very tired was found to be a significant predictor of testing positive for SARS-CoV-2 (p = 0.02). GBA genotype, as a surrogate indicator of mild or moderate/severe GD phenotype, was not associated with the

### Table 1
Demographics, comorbidities, and GD treatment of the full study cohort (n = 181).

| Characteristic                  | All patients (N = 181) | Pediatric (N = 31) | Adult (N = 150) |
|--------------------------------|------------------------|--------------------|-----------------|
| Demographics                   |                        |                    |                 |
| Age, mean (sd), y              | 43 (21.7)              | 8.5 (4.5)          | 50.1 (16.2)     |
| Sex, Females, no. (%)          | 83 (46)                | 15 (48)            | 68 (45)         |
| AJ Ancestry, no. (%)           | 154 (85)               | 25 (81)            | 129 (86)        |
| GBA N370S/N370S, no. (%)       | 110 (61)               | 16 (52)            | 94 (63)         |
| BMI, mean (sd)                 | N/A                    | N/A                | 26.5 (4.6)      |
| No. of COVID-19 Symptoms, mean (sd) | 0.7 (1.7)         | 0.4 (0.6)          | 0.8 (1.8)       |
| No. of Comorbidities, mean (sd) | 0.7 (1.0)             | 0.2 (0.6)          | 0.8 (1.0)       |
| Comorbidities, no. (%)         |                        |                    |                 |
| High blood pressure            | 24 (13)                | –                  | 24 (16)         |
| Diabetes                       | 4 (2)                  | –                  | 4 (3)           |
| Overweight                     | 9 (5)                  | –                  | 9 (6)           |
| Lung disease                   | 3 (2)                  | –                  | 3 (2)           |
| Liver disease                  | 3 (2)                  | 1 (3)              | 2 (1)           |
| Kidney disease                 | 2 (1)                  | –                  | 2 (1)           |
| History of cancer              | 11 (6)                 | –                  | 11 (7)          |
| Immune disease                 | 2 (1)                  | –                  | 2 (1)           |
| History of smoking             | 7 (4)                  | –                  | 7 (5)           |
| Parkinson’s disease            | 5 (3)                  | –                  | 5 (3)           |
| Heart disease                  | 12 (7)                 | 1 (3)              | 11 (7)          |
| Other                          | 32 (18)                | 4 (13)             | 28 (19)         |
| Treatment                      |                        |                    |                 |
| Current GD Treatment, no. (%)  | 127 (70)               | 10 (32)            | 117 (78)        |
| - ERTa                         | 86 (48)                | 9 (29)             | 77 (51)         |
| - SRTb                         | 41 (23)                | 1 (3)              | 40 (27)         |
| Total Years of Tx, mean (sd), y| 16.5 (9.3)             | 5.3 (3.3)          | 17.3 (9.1)      |

### Table 2
Demographics, comorbidities, and GD treatment of a subset of adults tested for SARS-CoV-2 by serology or nucleic acid testing (n = 88).

| Characteristic                  | Tested Positive (n = 16) | Tested Negative (n = 72) | Comparison between Positive-Negative (P) |
|--------------------------------|--------------------------|--------------------------|----------------------------------------|
| Demographics                   |                          |                          |                                        |
| Age, mean (sd), y              | 49.8 (15.1)              | 51.7 (17.9)              | 0.7                                     |
| Sex, Females, no. (%)          | 10 (11)                  | 27 (31)                  | 0.07                                    |
| AJ Ancestry, no. (%)           | 15 (17)                  | 63 (72)                  | 0.99                                    |
| GBA N370S/N370S, no. (%)       | 13 (15)                  | 47 (53)                  | 0.99                                    |
| BMI, mean (sd)                 | 27.8 (5.8)               | 26.4 (4.5)               | 0.3                                     |
| No. of COVID-19                | 4.4 (2.4)                | 0.3 (1.2)                | <0.0001                                 |
| Symptoms, mean (sd)            |                          |                          |                                        |
| No. of Comorbidities, mean (sd)| 0.6 (1.0)               | 0.9 (1.1)                | 0.3                                     |
| Comorbidities, no. (%)         |                          |                          |                                        |
| High blood pressure            | 3 (3)                    | 13 (15)                  | 0.95                                    |
| Diabetes                       | –                        | 2 (2)                    | –                                       |
| Overweight                     | –                        | 6 (7)                    | –                                       |
| Lung disease                   | –                        | 2 (2)                    | –                                       |
| Liver disease                  | 1 (1)                    | 1 (1)                    | 0.3                                     |
| Kidney disease                 | –                        | 2 (2)                    | –                                       |
| History of cancer              | 1 (1)                    | 7 (8)                    | 0.7                                     |
| Immune disease                 | –                        | 1 (1)                    | –                                       |
| History of smoking             | –                        | 6 (7)                    | –                                       |
| Parkinson’s disease            | 1 (1)                    | 1 (1)                    | 0.3                                     |
| Heart disease                  | 1 (1)                    | 7 (8)                    | 0.7                                     |
| Other                          | 2 (2)                    | 11 (13)                  | 0.8                                     |
| Treatment                      |                          |                          |                                        |
| Current GD Treatment, no. (%)  | 11 (13)                  | 58 (66)                  | 0.3                                     |
| - ERTa                         | 9 (13)                   | 45 (65)                  | 0.3                                     |
| - SRTb                         | 2 (3)                    | 13 (19)                  | –                                       |
| Total Years of Tx, mean (sd), y| 17.6 (8.4)               | 16.2 (10.3)              | 0.9                                     |

AJ indicates Ashkenazi Jewish; BMI, body mass index; and Tx, treatment.

* Percentages in these columns are in reference to total number of patients tested.

* ERT included imiglucerase, velaglucerase alfa, taliglucerase alfa.

* SRT included eliglustat.

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probability of either being symptomatic or testing positive. Being on GD therapy or the use of SRT compared to ERT did not affect being symptomatic for COVID-19 or testing positive for SARS-CoV-2.

### Discussion

To our knowledge, this is the first study to systematically evaluate SARS-CoV-2 infections in GD patients during the peak of the 2020 pandemic. Previous reports from Israel [22] and Europe [23,24] indicated that there were isolated reports of GD patients with symptoms suggestive of COVID-19, but no confirmatory evidence of infection or determinants of infection. One third of adults with GD included in this study reported being exposed to SARS-CoV-2, however it is reassuring that the majority of them did not report any symptoms. In our cohort, reported being exposed to SARS-CoV-2, however it is reassuring that these 3 patients were included 40 adults taking eliglustat, a glucosylceramide synthase inhibitor, as SRT. Glucosylceramide synthase inhibitors were suggested to provide a protective effect by a previous report of an in vitro study [25], however we did not find our patients on eliglustat reported fewer symptoms or had a decreased probability of testing positive compared to those on ERT. Finally, we are reassured to find that GD with its chronic metabolic inflammatory state does not seem to be associated with severe outcomes of SARS-CoV-2 infection. In GD, there is polarization of NKT cells towards THF phenotype and B cell lymphoproliferation which may facilitate antibody formation in setting of SARS-CoV-2 infection [26]. Indeed, among 9 patients who seroconverted and had quantitative serology testing, the antibody titers are moderate to high in keeping with a robust immune response [20]. Collection of serum and/or plasma samples would have been beneficial to assess levels of inflammatory biomarkers in these patients, but could not be accomplished due to the restrictions in place during the pandemic. This topic deserves further investigation. Limitations of our study include single center data collection and a relatively homogenous cohort of patients managed at a tertiary care center. Additionally, exposure to SARS-CoV-2 was self-reported and laboratory evidence of SARS-CoV-2 infection could only be assessed in 88/181 patients. Given the rapidly changing landscape of SARS-CoV-2 testing, including access and accuracy of testing at the time of this study.

### Table 3

Reported COVID-19 symptoms and signs and SARS-CoV-2 testing by GBA genotype group.

| Symptom/Meta | All patients (N = 181) | Type 1 GD (N = 121) | Type 2 GD (N = 57) |
|--------------|-----------------------|---------------------|--------------------|
| Any COVID-19 Symptoms, no. (%) | 45 (25) | 31 (26) | 14 (25) |
| Any 3+ COVID-19 Symptoms, no. (%) | 18 (10) | 14 (12) | 4 (7) |
| Cough | 17 (9) | 15 (12) | 2 (4) |
| Fever | 23 (13) | 18 (15) | 5 (9) |
| Chills, Night Sweats | 8 (4) | 6 (5) | 2 (4) |
| Very Tired | 16 (9) | 9 (7) | 7 (12) |
| Achy | 11 (6) | 7 (6) | 4 (7) |
| Abdominal pain | 1 (1) | - | 1 (2) |
| Diarrhea | 4 (2) | 4 (3) | - |
| Not able to taste | 6 (3) | 5 (4) | 1 (2) |
| Not able to smell | 7 (4) | 5 (4) | 2 (4) |
| Bruising | - | - | - |
| Chest pain | 2 (1) | 1 (1) | 1 (2) |
| Feeling short of breath | 4 (2) | 2 (2) | 2 (4) |
| COVID-19 toes | 1 (1) | 1 (1) | - |
| Extreme exhaustion | 8 (4) | 6 (5) | 2 (4) |
| Weakness | 13 (7) | 10 (8) | 3 (5) |
| Other | 8 (4) | 7 (6) | 1 (2) |
| SARS-CoV-2 testing, no. (%) | 77 (43) | 56 (46) | 21 (37) |
| NAT<sup>a</sup> | 34 (19) | 23 (19) | 11 (19) |
| a. NAT+ | 5 (16) | 5 (24) | - |
| a. 3+ symptoms | 5 (100) | 5 (100) | - |
| b. <3 symptoms | - | - | - |
| b. NAT- | 27 (84) | 16 (76) | 11 (100) |
| a. 3+ symptoms | 3 (11) | 3 (19) | - |
| b. <3 symptoms | 24 (89) | 13 (81) | 11 (100) |
| Antibody testing<sup>b</sup> | 61 (33) | 45 (37) | 16 (28) |
| a. Antibody+ | 15 (25) | 13 (30) | 2 (13) |
| a. 3+ symptoms | 9 (60) | 8 (62) | 1 (50) |
| b. <3 symptoms | 6 (40) | 5 (38) | 1 (50) |
| b. Antibody- | 42 (70) | 29 (66) | 13 (81) |
| a. 3+ symptoms | 3 (7) | 3 (10) | - |
| b. <3 symptoms | 39 (93) | 26 (90) | 13 (100) |

<sup>a</sup> All patients’ column includes 3 patients with Type 3 GD

<sup>b</sup> Other genotypes included: N370S/N44GG, N370S/L444P, N370S/D409H, N370S/IVS2+1, R496H/N44GG, N370S/G202R, N370S/R463H, N370S/V394L, R463C/R463G, R496H/IVS2+1, L444P/P198R.
we had limited details about testing modalities. Nevertheless, important information for clinical practice is gleaned from our analysis. With the increasing cases of SARS-CoV2 infection globally, providers treating patients with GD can utilize our data to counsel patients and guide clinical management. Our study addresses the important concerns raised during the initial phase of the pandemic [3] and should be reassuring to the larger GD community.

5. Conclusions

In summary, our data suggests that GD patients do not appear to have an increased risk for severe SARS-CoV-2 infection, despite additional risk factors. Further studies on the interaction of immunopathology and lysosomal dysfunction of GD vs SARS-CoV-2 infection should be illuminating to reveal, if in fact metabolic inflammation involving B cell lymphoproliferation and lysosomal dysfunction that underlies Gaucher disease pathophysiology, protects or otherwise modifies responses to SARS-CoV-2 infection.

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