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Letters to the Editor: New Observations

SARS-CoV-2-associated Guillain-Barré syndrome: a descriptive and comparative analysis

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The recent coronavirus disease (COVID-19) pandemic has placed an unprecedented burden on health care systems around the world, with extensive research directed on understanding its systemic implications in the human body. Multiple studies have described central nervous system affection as part of COVID-19 presentation.[1] Guillain-Barré syndrome (GBS) is an inflammatory disease of the peripheral nervous system involving a preceding infection that induces an aberrant autoimmune response. The recent pandemic caused by SARS-CoV-2 presents as a potential triggering factor of this entity, as various case reports have suggested an association of COVID-19 and GBS development.[2,3]

In this study, we describe the clinical characteristics of GBS presented in our tertiary referral center during the COVID-19 pandemic, with further focus on those associated with a previous SARS-CoV-2 infection.

This is a retrospective observational study. We recollected demographic, clinical, and paraclinical information of patients diagnosed with GBS hospitalized at the University Hospital Dr José E. González during the COVID-19 pandemic, from March to December 2020. Diagnosis of GBS was based on the Brighton criteria,[4] and patients were classified according to the results of SARS-CoV-2 diagnostic tests; patients with either positive antibody or PCR test were included in the SARS-CoV-2-related GBS (SC2-GBS) group.

Clinical batteries used for assessment included Hughes scoring system, applied at nadir of symptomatology and at discharge, Erasmus GBS Respiratory Insufficiency Score (EGRIS), applied during the first week of admission, Medical Research Council (MRC) sum score for muscle strength, applied at admission and at discharge, and modified Erasmus GBS Outcome Score (mEGOS), applied at the day 0 and 7 of admission.

A descriptive analysis was conducted with SPSS version 25 (IBM Corp, Armonk, NY). Data were tested for normality with Shapiro-Wilk test. Continuous variables are expressed as median (range) or mean ± standard deviation where appropriate. Categorical variables are expressed as absolute numbers and percentages. A comparative analysis of clinical and paraclinical characteristics was conducted between patients based on positivity to SARS-CoV-2 tests.

Seventeen patients were included during the study period; nine (53%) fulfilled level 1 and eight (47%) level 2 of Brighton criteria. Most of the population was female ($n = 10$, 58.8%). Mean age at diagnosis was 40.8 ± 18.7 years, and 10 (58.8%) patients had a history of infectious process prior to GBS onset; from these patients, 4 (40%) referred upper respiratory tract infection and 3 (30%) previous diarrheic episodes. Comorbidities were found in 35.2% of patients, mainly chronic arterial hypertension (23.5%), diabetes (11.8%), and obesity (11.8%).

Five (29.4%) patients from the total sample had a positive SARS-CoV-2 test by either PCR test or IgG/IgM titers; 1/5 had a positive PCR test only, 2/5 had positive IgG/IgM titers only, and 2/5 had both positive PCR test and IgG/IgM titers. From the SC2-GBS cases classified by positive IgG/IgM titers only (2/5), a viral prodrome characterized by mild fever, cough, myalgias, headache, and arthralgias preceded GBS symptoms by 16 and 28 days, respectively.

No significant differences were observed in sociodemographic nor in most clinical manifestations of patients with GBS in each group (see Table 1); only patients with negative SARS-CoV-2 test developed dysarthria as part of the clinical presentation (7/12, 58.3%). All patients in both groups presented with acute bilateral muscle weakness and experienced weakness and areflexia/hyporeflexia in upper and lower extremities. On the other side, cerebrospinal fluid analysis demonstrated non-significant differences in parameters between groups (see Table 2). Median cellularity was 0/mm^3 (0–8/mm^3) cells, whereas mean glucose and protein levels were 3.60 ± 0.63 mmol/L (reference values: 2.5–4.4 mmol/L) and 905 ± 892 mg/L (reference values: 150–450 mg/L), respectively. Regarding clinical batteries, no significant differences were observed in any scoring system between groups (see Table 2).

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Table 1: Initial clinical manifestations and at nadir of patients with SARS-CoV-2-related and unrelated Guillain-Barré syndrome

Variable	Total patients ($n = 17$)	SC2-GBS ($n = 5$)	Non-SC2-GBS ($n = 12$)	p
Clinical presentation				
Bilateral acute weakness, *n**	17 (100)	5 (100)	12 (100)	–
UE weakness, *n*	17 (100)	5 (100)	12 (100)	–
UE weakness, initial, *n*	6 (35.3)	2 (40)	4 (33.3)	0.60
LE weakness, *n*	17 (100)	5 (100)	12 (100)	–
LE weakness, initial, *n*	10 (58.8)	3 (60)	7 (58.3)	0.68
Areflexia/Hyporeflexia UE, *n*	17 (100)	5 (100)	12 (100)	–
Areflexia/Hyporeflexia UE, initial, *n*	5 (29.4)	2 (40)	3 (25)	0.47
Areflexia/Hyporeflexia LE, *n*	17 (100)	5 (100)	12 (100)	–
Areflexia/Hyporeflexia LE, initial, *n*	5 (29.4)	2 (40)	3 (25)	0.47
Sensorial abnormalities UE, *n*	11 (64.7)	3 (60)	8 (66.7)	0.60
Sensorial abnormalities UE, initial, *n*	5 (29.4)	0 (0)	5 (41.7)	0.12
Sensorial abnormalities LE, *n*	13 (76.5)	4 (80)	9 (75)	0.67
Sensorial abnormalities LE, initial, *n*	6 (35.3)	2 (40)	4 (33.3)	0.60
Bilateral facial paralysis, *n*	3 (17.6)	1 (20)	2 (16.7)	0.67
Bilateral facial paralysis, initial, *n*	0 (0)	0 (0)	0 (0)	–
Dysphagia, *n*	8 (47.1)	2 (40)	6 (50)	0.56
Dysphagia, initial, *n*	0 (0)	0 (0)	0 (0)	–
Dysarthria, *n*	7 (41.2)	0 (0)	7 (58.3)	**0.04**
Dysarthria, initial, *n*	0 (0)	0 (0)	0 (0)	–
Dyspnea, *n*	8 (47.1)	3 (60)	5 (41.7)	0.43
Dyspnea, initial, *n*	0 (0)	0 (0)	0 (0)	–
Dysautonomia, *n*	5 (29.4)	2 (40)	3 (25)	0.48
Dysautonomia, initial, *n*	0 (0)	0 (0)	0 (0)	0.70
Ophthalmoparesis, *n*	4 (23.5)	1 (20)	2 (16.7)	0.47
Ophthalmoparesis, initial, *n*	3 (17.6)	1 (20)	2 (16.7)	–
Ataxia, *n*	2 (11.8)	0 (0)	2 (16.7)	0.67
Ataxia, initial, *n*	1 (5.9)	0 (0)	1 (8.3)	0.67

SC2-GBS = SARS-CoV-2-related GBS; GBS = Guillain-Barré syndrome; UE = Upper extremity; LE = Lower extremity.
A p-value < 0.05 was considered significant.
*n (%).

Most patients with SC2-GBS received plasmapheresis (60%), whereas most patients in the other group received intravenous immunoglobulin (58.3%). At the end of study follow-up, 13 patients (76.4%) were discharged, 2 (11.7%) were transferred to other hospital, 1 (5.8%) remained hospitalized, and 1 (5.8%) died due to COVID-19-associated pneumonia. Electrophysiological studies were conducted in 12 patients (70.6%), the most frequent variant was AMAN (47.1%), followed by AIDP (17.6%). From the SC2-GBS patients, 2 had AMAN variant (40%), 2 AMSAN variant (40%), and 1 AIDP variant (20%).

We found no significant differences in sociodemographic and clinical characteristics between patients with SC2-GBS and patients with non-SC2-GBS. It is important to mention that other centers have observed an abnormal increase in admitted patients with GBS, with an also increased age at diagnosis (60 years) compared to pre-pandemic cases (mean 40 years).[5,6] Nonetheless, when comparing GBS cases admitted to our University Hospital in 2019 vs. 2020, no significant differences in the frequency of reported cases (21 vs. 21 cases/year) nor in the age at diagnosis (35.0 ± 19.9 vs. 38.4 ± 16.0) were noted. Rather than using the former as suggestive evidence for a non-association between COVID-19 and GBS, we believe this slight reduction in cases might be attributed to the effect of increased hand hygiene, social distancing, and the lockdown, as previously reported.[7]

Various systematic reviews of case reports regarding SC2-GBS have been published.[2,3] Two of these support our findings, demonstrating a resemblance between the SC2-GBS and the non-SC2-GBS presentation.[2,3] Nonetheless, the most recent review, which included 61 patients mostly of high- to middle-income countries, observed a high percentage (75.6%) of the classical demyelinating subtype, with most (65.3%) having a good outcome at discharge (Hughes ≤ 2).[3] Contrastingly, in our study, the most common electrophysiological findings in this population belonged to AMAN and AMSAN (80%) variants of GBS, with only 1 SC2-GBS patient with a AIDP variant (20%). A distinctive feature observed in systematic reviews of reported cases is the worse outcomes in SC2-GBS;[8] in our study, no significant differences were observed in Hughes score at discharge; however, the mortality rate in the SC2-GBS was 20% compared to 0% in the non-SC2-GBS group,

Table 2: Comparative analysis of cerebrospinal fluid parameters and clinical batteries of patients with SARS-CoV-2-related and unrelated Guillain-Barré syndrome

Variable	Total population ($n = 17$)	SC2-GBS ($n = 5$)	Non-SC2-GBS ($n = 12$)	p
CSF cellularity, median (range)*	0 (0–8)	0 (0–5)	0 (0–8)	0.45
CSF Protein level, mean (SD)**	905 (692)	1160 (606)	863 (746)	0.70
CSF glucose levels, mean (SD)***	3.6 (0.63)	3.4 (0.82)	3.5 (0.54)	0.36
CSF/serum glucose ratio	0.64 (0.0)	0.6 (0.0)	0.64 (0.1)	0.91
Hughes scoring system at nadir, median (range)	4 (4–5)	4 (4–5)	4 (4–5)	0.80
Hughes scoring system at discharge, median (range)	4 (2–6)	4 (2–6)	4 (2–4)	0.89
EGRIS, median (range)	4 (0–7)	3 (0–6)	4 (3–7)	0.15
mEGOS at admission, median (range)	6 (0–9)	5 (0–7)	6 (2–9)	0.14
mEGOS at day 7 of admission, median (range)	7 (0–12)	4 (0–10)	7.5 (0–12)	0.33
MRC sum score at admission, median (range)	28 (3–60)	36 (18–52)	28 (3–60)	0.25
MRC sum score at discharge, median (range)	36 (0–55)	44 (12–54)	35.5 (0–55)	0.51

SC2-GBS = SARS-CoV-2-related Guillain-Barré syndrome; CSF = cerebrospinal fluid; EGRIS = Erasmus GBS Respiratory Insufficiency Score; mEGOS= modified Erasmus GBS Outcome Score; MRC = Medical Research Council; SD = standard deviation.
*cells/mm^3.
**mg/L.
***mmol/L.

potentially supporting this observation. Nonetheless, the low sample size requires careful consideration.

Lastly, two similar studies described the natural history of GBS cases, both SC2-GBS and non-SC2-GBS, during the COVID-19 pandemic. One was conducted in an Italian region during the first months of the COVID-19 outbreak; however, the focus was mainly on management pitfalls attributed to the general health strategy at that time, and no direct comparison of clinical and paraclinical features was conducted.[9] The other was conducted in another center in Mexico, where 7/42 patients belonged to the SC2-GBS group, and no differences in clinical and paraclinical variables were observed in the comparative analysis, similar to our study.[10]

In conclusion, our study found no significant differences in the clinical presentation, clinical batteries, and CSF analysis between SC2-GBS and other non-SC2-GBS. Although COVID-19 outbreak did not correlate with an increase in GBS cases in our hospital compared to pre-pandemic years, the potential immunological association and molecular mimicry of SARS-CoV-2 with human proteins[11] shall be considered in its pathogenesis.

Conflict of Interest. The authors have no conflict of interest to report.

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