Guillain-Barré syndrome during COVID-19 pandemic: experience from a referral healthcare center in Mexico

Juan C. López-Hernández, Esther Y. Pérez-Valdez, Elizabeth León-Manríquez, Lisette Bazán-Rodríguez, Javier A. Galnares-Olalde, Adib Jorge-de Saráchaga, M. Eugenia Briseño-Godínez, Raúl N. May-Mas, Edwin S. Vargas-Cañas

Introduction. To describe clinical characteristics and electrophysiological variants of GBS cases during the pandemic, we carried out a comparative analysis between SARS-CoV2 related GBS and non-SARS-CoV2 patients and then compared to the 2019 cases.

Patients and methods. We carried out a cross-sectional study of GBS patients diagnosed according to Asbury and Cornblath criteria. We collected information on clinical and paraclinical variables. We defined a SARS-CoV-2 related GBS case according to the description of Ellul et al. We used Hadden criteria to classify the electrophysiological variants. We performed a comparative analysis between groups.

Results. Fourty-two patients were diagnosed with GBS in 2020, men 64.2%, age 46 ± 17.4 years, patients with obesity/overweight 42.8%, previous diarrhea 31%, history of respiratory tract infection 14.2%. Guillain Barre Disability Scale ≥ 3 points 71.4% and, cranial nerve involvement 69%. The most frequent electrophysiological variant was acute inflammatory demyelinating polyradiculoneuropathy (AIDP) 53.5%. Seven (16.6%) cases were SARS-CoV2 related, four men, age 43.4 ± 13.4 years. When comparing patients with GBS in 2020 vs patients in 2019, we observed a decrease in the previous infection history during 2020 (45.2% vs 73.3%, *p*-value = 0.005) and a decrease in previous respiratory infection (14.2% vs 33.3%, $p = 0.045$), as well as a higher frequency of cranial nerve involvement, and albuminocytologic dissociation.

Conclusions. SARS-CoV2 virus infection preventive measures may be impacting the presentation of post-infectious diseases such as GBS. We did not observe an increase in GBS cases during 2020. Also, the AIDP variant were more frequent in our population in the COVID-19 pandemic.

Key words. AIDP. Clinical presentation. Electrophysiological variant. Guillain-Barre syndrome. SARS-CoV-2 infection. SARS-CoV-2 pandemic.

Neuromuscular Diseases Department. Instituto Nacional de Neurología y Neurocirugía. Ciudad de México, Mexico.

Correspondence:
Dr. Edwin Steven Vargas-Cañas. Av. Insurgentes Sur, 3877. La Fama, Tlalpan. 14269 Ciudad de México, México.

E-mail:
clinicaneuromuscular.innn@gmail.com

ORCID:
0002-3198-5207

Accepted:
01.10.21.

How to cite this article:
López-Hernández JC, Pérez-Valdez EY, León-Manríquez E, Bazán-Rodríguez L, Galnares-Olalde JA, Jorge-de Saráchaga A, et al. Guillain-Barré syndrome during COVID-19 pandemic: experience from a referral healthcare center in Mexico. Rev Neurol 2021; 73: 315-20. doi: 10.33588/rn.7309.2021364.

Versión española disponible en www.neurologia.com

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was described for the first time in December 2019 as the cause of a respiratory illness known as COVID-19. Common neurological symptoms related to SARS-CoV-2 infection include headache, dizziness, confusion, myalgias, and anosmia [1]. Guillain Barré syndrome (GBS) is the most common cause of acute flaccid weakness worldwide, and it typically presents after a respiratory or gastrointestinal infection due to viral (cytomegalovirus or Epstein-Barr) or bacterial (*Campylobacter jejuni* or *Mycoplasma pneumoniae*) agents. Recently associated with the Zika pandemic [2].

Several reports have been published regarding the association of GBS and COVID-19 cases, although this relationship remains controversial [3,4]. Ellul et al described COVID-19 related GBS in all patients that initiate with GBS symptoms and a positive PCR/acute antibodies laboratory result within six weeks of SARS-CoV-2 infection [1]. European countries demonstrated a rise of GBS cases so far during the pandemic and reported 80% of these COVID-19 related [5,6].

The study of this etiopathogenic relationship in Latin America is limited to isolated case reports. In Mexico, social isolation and early symptom report remain the most applied measures to prevent SARS-CoV-2 transmission. Consequently, this has also reduced exposure to other respiratory transmitted infections and increased awareness when respiratory or gastrointestinal symptoms develop, leading to opportunistic health care access. This study describes clinical and epidemiological characteristics in GBS patients during the COVID-19 pandemic in our country.

Table I. Clinical and demographic characteristics of patients with GBS at the National Institute of Neurology and Neurosurgery.

	SGB patients 2020 *n* = 42	SGB patients 2019 *n* = 45	*p* value
Age (years) ± SD	46 ± 17.4	44.9 ± 19.4	0.79
Male, *n* (%)	27 (64.2)	30 (66.6)	0.82
Hypertension, *n* (%)	2 (4.7)	1 (2.2)	0.60
Obesity/overweight, *n* (%)	18 (42.8)	25 (55.5)	0.28
Previous infection history, *n* (%)	19 (45.2)	33 (73.3)	0.005
Respiratory tract infection, *n* (%)	6 (14.2)	15 (33.3)	0.045
Gastrointestinal infection, *n* (%)	13 (31)	18 (40)	0.37
MRC score at diagnosis ± SD	33.1 ± 17.8	30.8 ± 17.6	0.54
Hughes ≥ 3, *n* (%)	30 (71.4)	35 (77.7)	0.62
Cranial nerve involvement	29 (69)	22 (48.8)	0.13
Facial nerve, *n* (%)	24 (57.1)	18 (40)	0.045
Ocular nerves, *n* (%)	12 (28.5)	8 (17.7)	0.31
Bulbar nerves, *n* (%)	24 (57.1)	13 (28.8)	0.018
Autonomic dysfunction, *n* (%)	11 (26.1)	13 (28.8)	0.81
IMV requirement	13 (30.9)	15 (33.3)	> 0.99
GBS electrophysiological variants:			
AIDP, *n* (%)	15/28 (53.5)	17/43 (39.5)	0.33
Axonal, *n* (%)	12/28 (42.8)	21/43 (48.8)	0.62
Equivocal, *n* (%)	1/28 (3.6)	2/43 (4.6)	> 0.99
Inexcitable, *n* (%)	0/27 (0)	2/43 (4.6))	0.14
Albuminocytological dissociation, *n* (%)	24/35 (68.5%)	12/32 (37.5)	0.01
Treatment:			
Conservative, *n* (%)	11 (26.1)	9 (20)	0.16
IVIg, *n* (%)	20 (47.6)	30 (66.6)	
PE, *n* (%)	11 (26.1)	6 (13.3)	

AIDP: acute inflammatory demyelinating polyradiculoneuropathy; IMV: invasive mechanical ventilation; IQR: interquartile range; IVIg: intravenous immunoglobulin; PE: plasmapheresis exchange; SD: standard deviation.

Patients and methods

We conducted a single-center observational study, including all GBS diagnosed patients during 2020, according to the Asbury criteria [7]. We describe demographic characteristics, infection history, Medical Research Council (MRC) and GBS Disability Score (GDS) at diagnosis, cranial nerve involvement, need for invasive mechanical ventilation, dysautonomia. We also report treatment types (intravenous immunoglobulin, plasma exchange, or conservative treatment). In addition, we classified patients according to the World Health Organisation (WHO) criteria as obese or overweight.

The case definition of SARS-CoV-2 related GBS is according to the Ellul et al description of probable association: GBS symptoms onset within six weeks of acute infection; and either SARS-CoV-2 RNA detected in any sample or antibody evidence of acute SARS-CoV-2 infection; and no evidence of other commonly associated causes [1]. To demonstrate a rise or a plateau in the yearly GBS cases and characteristic clinical differences, we compared 2020 new cases and 2019 total cases.

We established electrophysiological variants according to Hadden criteria [8]. Additionally, we analyzed cerebrospinal fluid (CSF) and defined albuminocytologic dissociation as raised CSF protein levels (≥ 45 mg/dL) and a total white cell count of < 10 cells/μL. All subjects gave written informed consent to participate in the study. The local Ethics Committee approved the study protocol.

Statistical analysis

For descriptive analysis, we determined data distribution with the Kolmogorov-Smirnov test. Mean, standard deviation or median, and interquartile range according to distribution, categorical variables in frequencies and percentages. We applied the Mann-Whitney *U* test for nonparametric continuous variables, chi-square test, and Fisher's exact test for categorical variables; p-value ≤ 0.05 was considered significant. We performed statistical analysis with the SPSS version 22 program.

Results

Fourty-two patients were diagnosed with GBS in 2020. Twenty-six (64%) men. The mean age was 46 ± 17.4 years, 42.8% were obese, 31% had diarrhea history, and 14.2% upper respiratory infection. GBS disability score of ≥ 3 in 71.4%, 69% had cranial

nerve involvement, and 31% required mechanical ventilation. The most frequent electrophysiological variant was acute inflammatory demyelinating polyradiculoneuropathy (AIDP) (53.5%). The rest of the basic characteristics are in Table I.

Seven patients (16.6%) identified with SARS-CoV-2 related GBS. The mean age was 43.4 ± 13.4 years. Two patients had positive nasopharyngeal PCR tests and five positive IgM-specific antibodies against SARS-CoV-2. Three patients had mild respiratory symptoms that preceded GBS symptoms by 2, 17, and 30 days, respectively. The reported SARS-CoV-2-related neurological symptoms were headache [3], fever [2], anosmia, and dysgeusia [1]. The remaining four patients presented with acute flaccid weakness with no previous symptoms.

Two patients were diagnosed with the AIDP variant and two with the axonal variant. In addition, four patients presented albuminocytologic dissociation. The rest of the characteristics are in Table II. We show the monthly distribution of GBS cases and SARS-CoV-2 related ones in Figure 1. We observed a significant difference in the history of previous respiratory infection when comparing patients with SARS-CoV-2 related GBS with the general cases during 2020 (42.8% vs. 8.5%, p=0.04). Table 2 shows the rest of the variables that were not significant.

We observed a decrease in previous infection history during 2020 compared to the ones in 2019 (45.2% vs. 73.3%, p = 0.005) and a respiratory infection history decrease (14.2% vs. 33.3%, p = 0.045). Patients of 2020 had significantly greater cranial nerve involvement and greater albuminocytologic dissociation (68.5% vs. 37%, p = 0.01). Figure 2 presents the general distribution of patients with GBS in 2019 and 2020.

Discussion

GBS is a post-infectious autoimmune disease that produces antibodies directed against gangliosides found in the nerve. There is a detection of a specific anti-ganglioside antibody in up to 60% of cases. The primary antibodies described are GM1, GT1a, GD1a, and GQ1b [2,8,9].

There have been reports of SARS-CoV-2 associated GBS cases throughout the pandemic. There is controversy about whether there is an association, or it is only coexistence since there is no evidence of SARS-CoV-2 virus particles in CSF samples. However, one study reported a SARS-CoV-2 related GBS case positive to the anti-ganglioside GD1b. This

Table II. Clinical, demographic and electrophysiological characteristics in GBS and COVID-19 related GBS patients.

	No SARS- CoV-2 *n* = 35	SARS-CoV-2 *n* = 7	*p* value
Age (years) ± SD	44.5 ± 18.3	43.4 ± 13.4	0.86
Male, *n* (%)	23 (65.7)	4 (57.1)	0.68
Obesity/overweight, *n* (%)	12 (34.2)	1 (14.2)	0.03
Diabetes mellitus, *n* (%)	1 (2.8)	1 (14.2)	0.41
Hypertension, *n* (%)	2 (5.7)	1 (14.2)	0.43
Previous infecction history, *n* (%)	13 (37.1)	3 (42.8)	0.41
Respiratory tract infection, *n* (%)	3 (8.5)	3 (42.8)	0.04
Gastrointestinal infection, *n* (%)	10 (28.5)	0 (0)	0.16
MRC score at diagnosis, ±SD	34.7 ± 16.9	32.8 ± 17.8	0.75
Hughes ≥3, *n* (%)	24 (68.5)	6 (85.7)	0.65
Cranial nerve involvement	23 (65.7)	4 (57.1)	0.68
Facial nerve, *n* (%)	18 (51.4)	4 (57.1)	> 0.99
Ocular nerves, *n* (%)	11 (31.4)	0 (0)	0.16
Bulbar nerves, *n* (%)	19 (54.2)	4 (57.1)	> 0.99
Autonomic dysfunction, *n* (%)	9 (25.7)	2 (28.5)	> 0.99
IMV requirement	11 (31.4)	2 (28.5)	> 0.99
GBS clinical variants:			
Sensorimotor, *n* (%)	25 (71.4)	5 (71.4)	> 0.99
Pure motor, *n* (%)	5 (14.2)	2 (28.5)	0.57
Miller Fisher/overlap syndrome, *n* (%)	4 (11.4)	0 (0)	> 0.99
GBS electrophysiological variants:			
AIDP, *n* (%)	12/23 (52.1)	2/4 (50)	> 0.99
AMAN, *n* (%)	8/23 (34.7)	1/4 (25)	> 0.99
AMSAN, *n* (%)	2/23 (8.6)	1/4 (25)	0.39
Equivocal, *n* (%)	1/23 (4.3)	0/5 (0)	> 0.99
Albuminocytological dissociation, n (%)	20/30 (66.6)	4/5 (80)	0.19
Proteins (mg/dL), median (IQR)	49 (32.5-91.5)	68 (42.5-79)	0.43

Table II. Clinical, demographic and electrophysiological characteristics in GBS and COVID-19 related GBS patients (cont.).

	No SARS- CoV-2 *n* = 35	SARS-CoV-2 *n* = 7	*p* value
Treatment:			
Conservative, n (%)	9 (25.7)	2 (28.5)	0.96
IV Ig, n (%)	17 (48.5)	3 (42.8)	
PE, n (%)	9 (25.7)	2 (28.5)	

AIDP: acute inflammatory demyelinating polyradiculoneuropathy; AMAN: acute motor axonal neuropathy; AMSAN: acute motor and sensitive axonal neuropathy; IMV: invasive mechanical ventilation; IQR: interquartile range; IVIg: intravenous immunoglobulin; PE: plasmapheresis exchange; SD: standard deviation.

Figure 1. Quarterly Guillain-Barré syndrome general cases and SARS-CoV-2 related one during 2020.

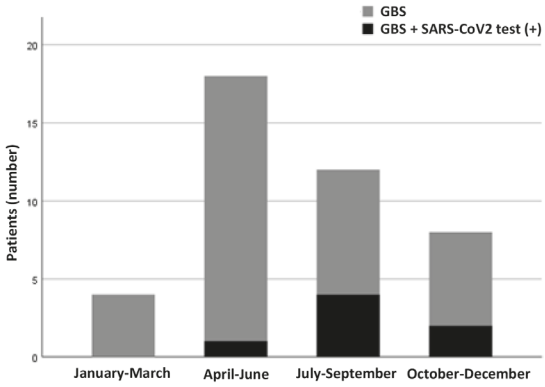
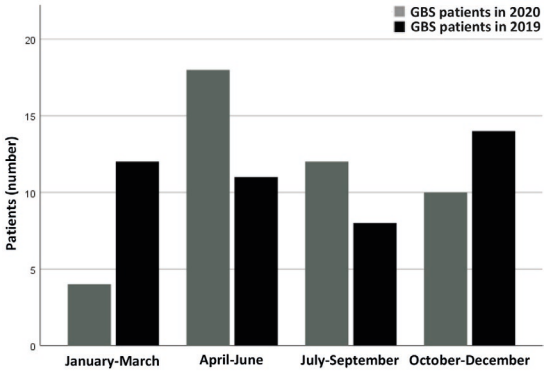


Figure 2. Quarterly comparison between 2019 and 2020 total Guillain-Barré syndrome cases.



finding provides information about the possible pathophysiological mechanism of SARS-CoV-2 associated GBS. Ganglioside GD1b contains sialic acid molecules within its molecular structure, the SARS-CoV2 peak (S) viral protein binds to sialic acid as an entry mechanism to the nervous system [3].

The worldwide GBS incidence is up to 0.89-1.81 cases per 100,000 inhabitants [2]. However, there has been an incidence increase during epidemiological events, the most recent being in 2016 with the Zika virus pandemic, which mainly affected French Polynesia and Latin American countries [10]. In March 2020, COVID-19 was declared a pandemic by the WHO. During this year, there is a report of more than 70 SARS-CoV-2 associated GBS cases have. However, the GBS incidence changes in different populations are controversial [10,11]. A study conducted in the United Kingdom reports no changes in GBS incidence from March to May 2020 [12]. Another study carried out in Italy showed an increase in GBS incidence of 0.202/100,000 from March to April 2020, reporting 34 GBS patients during this time. 88.2% of these patients had a positive test for SARS-CoV-2 (nasopharyngeal PCR or specific antibody) [5].

We know in advance that this is not an epidemiological study, but in our center, 16.6% of GBS patients seen during 2020 were SARS-CoV-2 associated, and we did not observe an increase in cases compared to 2019. We take this information with reserve because it is a single-center report. Nevertheless, it represents a great sample of what is happening in our country.

In Mexico, social isolation and hygiene measures were implemented and promoted to prevent the spread of the SARS-CoV-2 virus. These measures had a direct impact on the epidemiology of seasonal infections across different populations. Up to 60% of GBS patients have an infectious event history within four weeks of the disease. Interestingly, we observed a decrease in the frequency of a history of both diarrhea and respiratory tract infections during 2020 compared to 2019 in our population [2].

The axonal variant, particularly acute motor axonal neuropathy (AMAN), is the most common GBS subtype in Mexico [13]. However, this last year, the most frequently encountered electrophysiological variant was AIDP (52.1%). One limitation of this study is that we performed most nerve conduction studies outside the COVID-19 contagious phase and delayed some in suspected cases for protective measures.

In 2020, GBS patients with demyelinating features presented more frequently, likewise cranial

nerve involvement and albuminocytologic dissociation [2,5]. We theorize that these epidemiological changes observed in our population, both the increase in AIDP variant presentation and decrease in diarrhea history, were due to the hygiene measures implemented to prevent SARS-CoV-2 virus transmission.

Almost all clinical variants have been described as possibly or probably associated with SARS-CoV-2 infection (sensorimotor, pure motor, and Miller Fisher syndrome and both AIDP and AMAN), along with more significant treatment responses IVIG or plasma exchange [11,14-15]. In our center, seven patients had GBS and a positive test for the SARS-CoV-2 virus. Our patients had similar clinical characteristics compared to other reports. We did not observe differences in GBS severity regarding clinical presentation, such as a GBS Disability Scale ≥ 3, mechanical ventilation requirement, or low MRC score at admission.

Risk factors for severe SARS-CoV-2 infection include diabetes, hypertension, and obesity [16,17]. All of them are significant health problems in our country due to their high prevalence in all age groups. We observed frequencies of 42-55% of GBS patients in the years 2019 and 2020. However, only one patient with SARS-CoV-2 related GBS had obesity and only presented the neurological clinical picture on admission without respiratory infection history.

SARS-CoV2 virus infection preventive measures are impacting the clinical presentation and characteristics of post-infectious diseases such as GBS. We did not observe an increase in GBS cases during 2020, but interestingly the AIDP variant and demyelinating clinical features were more frequent in our population during the COVID-19 pandemic. Moreover, extensive descriptions are needed in other countries to achieve a better understanding of these issues.

References

1. Ellul M, Benjamin L, Singh B, Lant S, Michael B, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol 2020; 19: 767-83.
2. Van den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs B, Van Doorn P. Guillain-Barré syndrome: pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol 2014; 10: 469-82.
3. Dalakas MC. Guillain-Barré syndrome: the first documented COVID-19-triggered autoimmune neurologic disease: more to come with myositis in the offing. Neurol Neuroimmunol Neuroinflamm 2020; 7: e781.
4. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni M, et al. Guillain-Barré syndrome associated with SARS-CoV-2. N Engl J Med 2020; 382: 2574-6.
5. Filosto M, Cotti Piccinelli S, Gazzina S, Foresti C, Frigeni B, Servalli M, et al. Guillain-Barré syndrome and COVID-19: an observational multicentre study from two Italian hotspot regions. J Neurol Neurosurg Psychiatry 2021; 92: 751-6.
6. Kuwabara S, Yuki N. Axonal Guillain-Barré syndrome: concepts and controversies. Lancet Neurol 2013; 12: 1180-8.
7. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990; 27 (Suppl): S21-4.
8. Hughes RA, Newsom-Davis JM, Perkin GD, Pierce JM. Controlled trial prednisolone in acute polyneuropathy. Lancet 1978; 2: 750-3.
9. Yuki N, Hartung HP. Guillain-Barré syndrome. N Engl J Med 2012; 366: 2294-304.
10. Capasso A, Ompad DC, Vieira DL, Wilder-Smith A, Tozan Y. Incidence of Guillain-Barré Syndrome (GBS) in Latin America and the Caribbean before and during the 2015-2016 Zika virus epidemic: a systematic review and meta-analysis. PLoS Negl Trop Dis 2019; 13: e0007622.
11. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. J Neurol 2021; 268: 1133-70.
12. Keddie S, Pakpoor J, Mousele C, Pipis M, Machado P, Foster M, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. Brain 2021; 144: 682-93.
13. López-Hernández JC, Colunga-Lozano LE, Garcia-Trejo S, Gómez-Figueroa E, Delado-Garcia G, Bazán-Rodriguez L, et al. Electrophysiological subtypes and associated prognosis factors of Mexican adults diagnosed with Guillain-Barré syndrome, a single center experience. J Clin Neurosci 2020; 80: 292-7.
14. Matsui N, Nodera H, Kuzume D, Iwasa N, Unai Y, Sakai W, et al. Guillain-Barré syndrome in a local area in Japan, 2006-2015: an epidemiological and clinical study of 108 patients. Eur J Neurol 2018; 25: 718-24.
15. Reyes-Bueno JA, García-Trujillo L, Urbaneja P, Ciano-Petersen N, Postigo-Pozo M, Martnez-Tomas C, et al. Miller-Fisher syndrome after SARS-CoV-2 infection. Eur J Neurol 2020; 27: 1759-61.
16. Guan WJ, Ni ZY, Hu Y, China Medical Treatment Expert Group for Covid-19, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382: 1708-20.
17. ENSANUT. México city; 2018 [March 2021]. Available from: https: //ensanut.insp.mx/encuestas/ensanut2018/doctos/informes/ensanut_2018_presentacion_resultados.pdf. Last consultation date: 07.08.2021.

Síndrome de Guillain-Barré durante la pandemia de COVID-19: experiencia de un centro de referencia en México

Introducción. Se trata de describir las características clínicas y variantes electrofisiológicas de los casos de síndrome de Guillain-Barré (SGB) durante la pandemia. Llevamos a cabo un análisis comparativo entre pacientes con SGB relacionado con el SARS-CoV-2 y sin antecedente del virus, y posteriormente realizamos una comparación con los casos de 2019.

Pacientes y métodos. Se llevó a cabo un estudio transversal de los pacientes con diagnóstico de SGB según los criterios de Asbury y Cornblath. Se recolectaron información clínica y variables paraclínicas. Definimos el SGB relacionado con el SARS-CoV-2 conforme a la descripción de Ellul et al. Se utilizaron los criterios de Hadden para la clasificación de las variantes electrofisiológicas. Por último, realizamos un análisis comparativo entre grupos.

Resultados. Se diagnosticó a 42 pacientes con SGB en 2020, un 64,2% hombres, con una edad de 46 ± 17,4 años, un 42,8% con obesidad/sobrepeso, un 31% con historia de diarrea previa y un 14,2% con infección respiratoria previa. El 71,4% tuvo una puntuación en la *Guillain-Barré Disability Score* igual o mayor que 3 puntos y el 69% tenía afectados los nervios del cráneo. La variante electrofisiológica más común fue la polirradiculoneuropatía desmielinizante inflamatoria aguda (PDIA; 53,5%). Siete (16,6%) casos tuvieron relación con el SARS-CoV-2, cuatro hombres, con edad de 43,4 ± 13,4 años. Al realizar la comparación entre pacientes con SGB de 2020 frente a los de 2019, observamos un decremento en el antecedente de infección previa en 2020 (45,2 frente a 73,3%; p = 0,005) y un decremento específico en la historia de infección respiratoria (14,2 frente a 33,3%; p = 0,045), así como una mayor frecuencia de afectación de los nervios del cráneo y de disociación albuminocitológica.

Conclusiones. Las maniobras preventivas para la infección por el SARS-CoV-2 impactan directamente en la presentación de enfermedades postinfecciosas como el SGB. No observamos un incremento en los casos de SGB durante 2020. Asimismo, la variante de PDIA fue la más frecuente en nuestra población durante la pandemia de COVID-19.

Palabras clave. Infección por el SARS-CoV-2. Pandemia de COVID-19. PDIA. Presentación clínica. Síndrome de Guillain-Barré. Variante electrofisiológica.