Rev Med Chile 2021; 149: 1812-1816

Guillain-Barré syndrome in patients with SARS-CoV-2 infection. Report of three cases

GABRIEL CEA[1,2], CRISTIAN ROMERO[2], SHIRLEY AGUILAR[2], RODRIGO SALINAS[1,2]

[1]Departamento de Ciencias Neurológicas, Facultad de Medicina, Universidad de Chile, Santiago, Chile.
[2]Servicio de Neurología, Hospital del Salvador, Servicio de Salud Metropolitano Oriente, Santiago, Chile.

Financial support: This work did not have any financial support or any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Declarations of interest: none.

Recibido el 22 de julio de 2021, aceptado el 4 de enero de 2022.

Corresponding author:
Gabriel Cea
Departamento de Ciencias Neurológicas, Universidad de Chile, Avenida JM Infante 533, Santiago, Chile.
jcea@med.uchile.cl

ABSTRACT

Several cases of Guillain Barre Syndrome (GBS) associated with SARS-CoV-2 have been published, most being acute inflammatory demyelinating polyradiculoneuropathy. Between April and December 2020, 1,499 cases of SARS-CoV-2 infection were admitted to Hospital del Salvador, in Santiago, Chile, serving a population of 521,920 adults. In the same period, seven cases of GBS were admitted. Three females had a demyelinated type of GBS associated with SARS-CoV-2 infection. All three presented with progressive flaccid symmetrical areflexic weakness with inability to walk, one needed intubation and mechanical ventilation due to SARS-CoV2 infection. All had a favorable, rapid response to intravenous immunoglobulin. In two patients, the onset of GBS was almost concomitant with SARS-CoV-2 infection. A causal relationship between SARS-CoV-2 and GBS has been questioned since no increase of GBS has occurred during the pandemic. However, a rise in GBS associated with SARS-CoV-2 infection could be hidden due to a general decrease of GBS due to the decrease of all other infections. Lack of reporting due to the pandemic could be an added factor.

(Rev Med Chile 2021; 149: 1812-1816)

Key words: *Guillain-Barre Syndrome; SARS-CoV-2; Pandemics; Chile.*

Síndrome de Guillain-Barré en pacientes con infección por SARS-CoV-2. Reporte de tres casos

Se han publicado varios casos de síndrome de Guillain Barre (SGB) asociados con el SARS-CoV-2, la mayoría de los cuales son polirradiculoneuropatía desmielinizante inflamatoria aguda. Entre abril y diciembre de 2020, se ingresaron 1.499 casos de infección por SARS-CoV-2 en el Hospital del Salvador de Santiago de Chile, que atiende a una población de 521.920 adultos. Durante el mismo período se admitieron siete casos de SGB. Tres pacientes de sexo femenino con SGB tipo desmielinizante asociado a una infección por SARS-CoV-2. Las tres presentaron debilidad simétrica, flácida y arrefléctica progresiva, con incapacidad para caminar, una necesitó intubación y ventilación mecánica debido a la infección por SARS-CoV2. Todas tuvieron una respuesta rápida y favorable a la inmunoglobulina intravenosa. En dos pacientes, la aparición de SGB fue casi concomitante con la infección por SARS-CoV-2. Una relación causal entre

el SARS-CoV-2 y SGB ha sido cuestionada ya que no se ha producido ningún aumento de SGB durante la pandemia. Sin embargo, un aumento de SGB asociado con la infección por SARS-CoV-2 podría ocultarse en una disminución general de SGB debido a la disminución de todas las demás infecciones asociadas a este. La sub-notificación debido a la dimensión de la pandemia podría ser también un factor.

Palabras clave: *Síndrome de Guillain-Barré; SARS-CoV-2; Pandemias; Chile.*

There is growing evidence that SARS-CoV-2 infection can be associated with neurological symptoms and complications, such as anosmia, dysgeusia, encephalopathy, encephalitis, stroke, acute peripheral nerve disease and myopathy[1]. Several cases of Guillain-Barré Syndrome (GBS) associated with SARS-CoV-2 have been reported, mostly acute inflammatory demyelinating polyradiculoneuropathy (AIDP), but acute motor axonal neuropathy (AMAN), and Miller-Fisher variant have also been described[2,3]. The first cases of SARS-CoV-2 in Chile were diagnosed in March 2020 and the first peak of daily cases appeared in July 2020. By December 2020, 608,973 SARS-CoV-2 cases had been diagnosed in Chile, with 16,608 deaths reported.

Between April and December 2020, 1,499 cases of SARS-CoV-2 were admitted to Hospital del Salvador, a public hospital in a South-East area of Santiago, Chile. This hospital serves a population of 521920 people aged 15 years or older[4]. During 2020, seven cases of GBS were admitted to our hospital, which is the usual number per year[5]. Five of them were admitted between April and December, three cases of GBS occurred in patients who were diagnosed with SARS-CoV-2 infection at time of admission. These cases are described below, and data summarized in Table 1. The study received ethics approval from our local Research Ethics Committee and each patient signed an informed consent.

Case 1

A forty-eight-year-old female was admitted to the emergency department in May 2020 with a five day history of progressive ascending leg weakness that made her unable to walk and without sphincter dysfunction. On examination she presented a flaccid, symmetrical, hypotonic predominantly distal tetraparesis, areflexic with flexor plantar response. There was no sensory level. A nasopharyngeal mucosal PCR swab test was positive for SARS-CoV-2 on admission. She had a past medical history of poorly controlled diabetes mellitus type 2 with polyneuropathy and liver failure secondary to fatty liver disease. Five days after developing progressive limb weakness she experienced ventilatory distress but did not require mechanical ventilation although a high flow cannula was necessary. A chest CT scan showed multifocal pneumonia with ground glass opacities. Cerebrospinal fluid analysis, on day 5 of her neurological symptoms, revealed normal results with protein 0.41 g/L, 2 white cells cells/mm^3 and glucose 1.03 gr/Lt. Serological tests for *human immunodeficiency virus* (HIV) and *hepatitis B and C* were negative. Due to the critical condition of the patient, electrophysiological study was not possible. She was started on intravenous immunoglobulin (IVIg) 2 gr/Kg over 5 days, with a favourable response and by the time she was discharged, she was able to walk. A month after discharge, electrophysiological studies showed a severe mixed polyneuropathy with prolonged distal latencies and delay in conduction velocity in both tibial nerves, compatible with demyelinating polyneuropathy, in addition to signs of pre-existing peripheral polyneuropathy.

Case 2

A thirty-one-year-old female was admitted in coma to the emergency department in June 2020. She had no previous medical history. Blood tests showed diabetic ketoacidosis and diabetes mellitus type 1 was diagnosed. A nasopharyngeal mucosal PCR swab test was positive for SARS-CoV-2 on admission. Brain CT scan was normal and chest CT scan showed multilobe pneumonia

and typical ground glass lesions. She had ventilatory failure and was admitted to the intensive care unit (ICU) and required mechanical ventilation. After 6 days an attempt to extubate failed requiring reintubation and mechanical ventilation. Four days later, when she was finally extubated, examination showed a hypophonic voice, generalized weakness, facial diplegia, tongue paresis and hypotonic weakness of all four limbs with areflexia and flexor plantar response. There was no sensory involvement. Cerebrospinal fluid analysis showed protein 1.80 g/L, 5 white cells cells/mm^3 and glucose 0.87 g/L. Serology for HIV and FilmArray™ were negative. Conduction velocity studies showed a pure motor demyelinated polyneuropathy and electromyography revealed no signs of denervation and poor recruitment pattern on effort. IVIg 2 gr/Kg over 5 days was given with a favorable response and the patient was able to walk by the ninth day after finishing this intervention.

Case 3

A sixty-two-year-old lady was admitted to hospital in October 2020, with a history of 12 days of fever, cough, and dyspnea. A nasopharyngeal mucosal PCR swab test was positive for SARS-CoV-2 on admission. She had a past medical history of non-specific colitis that had been treated with mesalazine and a mild to moderate sensory polyneuropathy. Chest CT scan showed pneumonia with ground glass opacities. She did not require mechanical ventilation and was discharged seven days later. Seven days after discharge she developed paresthesia in both legs, progressive weakness of all limbs, more pronounced in the legs, and severe dorso-lumbar back pain. Eight days later she was unable to walk and returned to the emergency department. On readmission she was afebrile and with no dyspnea. She had facial diplegia, weakness in upper and lower limbs, areflexia, a flexor plantar response, and multimodal

Table 1. Clinical and tests summary of GBS patients associated with SARS-CoV-2

	Case 1	Case 2	Case 3
Gender	F	F	F
Age (years)	48	31	62
Pharyngeal PCR SARS-CoV-2 on admission	Positive	Positive	Positive
Mechanical ventilation	No	Yes	No
Electrophysiological study	Demyelinating polyneuropathy - CV 27 and 30 m/s - Absent F waves - Absent tibial H reflexes Additional signs of pre-existing peripheral polyneuropathy	Demyelinating polyneuropathy - CV 28 and 38 m/s - Absent F waves - Absent tibial H reflexes Normal sensory study	Demyelinating polyneuropathy - CV 36 and 39 m/s - F 57.3 and 63.4 ms - Absent tibial H reflexes Pre-existing mild signs of sensory polyneuropathy
Chest CT scan	Multifocal pneumonia/ground glass opacities	Multifocal pneumonia/ground glass opacities	Pneumonia/ground glass opacities
CSF study	2 white cells/mm^3 Protein 0.41 g/L Glucose 1.03 g/L	5 white cells/mm^3 Protein 1.8 g/L Glucose 0.87 g/L	1 white cell/mm^3 Protein 0.61 g/L Glucose 0.64 g/L
Treatment	IV immunoglobulin 2 gr/Kg over 5 days	IV immunoglobulin 2 gr/Kg over 5 days	IV immunoglobulin 2 gr/Kg over 5 days
Microbiology study	HIV (-) Hepatitis B-C (-)	HIV (-) FilmArray™ (-)	Not performed

(-): negative; IV: intravenous; HIV: human immunodeficiency virus; CSF: cerebrospinal fluid; CT: computerized tomography; FilmArray™: multiplex polymerase chain reaction film that includes 14 respiratory, bacterial and yeast microorganisms; m/s: meters per seconds; CV: conduction velocity; ms: milliseconds.

hypoesthesia in both legs. Cerebrospinal fluid analysis showed protein 0.61 g/L, 1 white cells/mm^3 and glucose 0.64 g/L. She was admitted to ICU and treated with IVIg 2 gr/Kg over 5 days with improvement of her muscle strength, although by the eighth day after starting treatment she was still unable to walk. Electrophysiological studies on the eighth day of symptoms showed a demyelinating pattern in all four limbs and electromyography showed a rather poor recruitment pattern but no sign of denervation.

Discussion

We report three clinical cases compatible with the demyelinating variant of GBS, two of them occurring during SARS-CoV-2 infection. All of them presented with flaccid symmetrical areflexic weakness with inability to walk, one case needed intubation and mechanical ventilation due to severe SARS-CoV-2 infection. All had a favorable and rapid response to IVIg, with notorious recovery of muscle strength before discharge. A review of cases of GBS associated with SAR-CoV-2 published in the literature has shown common features that were present in our cases[6]. Most published cases were of the demyelinating type, showed a good response to IVIG, and fatal cases were related to complications of SARS-CoV-2 infection rather than to GBS.

About two-thirds of cases of GBS are post-infectious, with the onset occurring within four to six weeks of a respiratory or gastrointestinal infection[7]. But in a variable proportion of patients, GBS is para-infectious, with the start of symptoms occurring during the infectious stage, as in two of our patients[8]. The physio-pathological mechanism of para-infectious GBS is unknown but an immune mechanism not related to molecular mimicry produced by an infectious agent or direct viral damage has been postulated[9,10]. Also, there may be some kind of sequential immune stimulation cross-reacting with previous infections such as has been proposed for arboviruses and Campylobacter jejuni[9]. Recent evidence of immunological memory for epitopes of SARS-CoV-2 in serum of people unexposed to this virus makes this hypothesis plausible[11].

Cases of GBS associated with SARS-CoV-2 infection have been reported in several countries, but in most countries, there are no reports. In Latin America, as far as we know, cases have been reported only in Brazil[12]. There is a high probability of under-reporting, as medical teams collapse under the pressure of caring for SARS patients. A causal relationship between SARS-CoV-2 and GBS has been questioned for several reasons[13]. Firstly, it has been argued that no peak increase in GBS has been detected during the peak time of SARS-CoV-2 pandemic, as apparently occurred during the Zika virus epidemic[14]. Secondly, there was no increase in incidence of GBS during the first wave of the pandemic[13]. However, a rise in GBS associated with SARS-CoV-2 infection could be hidden in a general decrease of GBS due to the decrease of all infections particularly seasonal air borne infections and Campylobacter jejuni usually associated with GBS[15,16]. SARS-CoV-2 has been implicated almost in absence of other infections associated with GBS[16].

We present this case series and feel that it is too early to state that there is not a causal relationship between SARS-Cov-2 and GBS. There should be more careful epidemiological surveillance and reporting of cases should be encouraged.

Acknowledgements: We are grateful to Dra. Philippa Moore for her invaluable help in reading and correcting the manuscript.

References

1. Whittaker A, Anson M, Harky A. Neurological Manifestations of COVID-19: A systematic review and current update. Acta Neurol Scand. [Internet] 2020 [cited 2020 Nov 23]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7273036/
2. Marta-Enguita J, Rubio-Baines I, Gastón-Zubimendi I. Síndrome de Guillain-Barré fatal tras infección por el virus SARS-CoV-2. Neurologia [Internet]. 2020 [cited 2020 Nov 23]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7166023/
3. Ray A. Miller Fisher syndrome and COVID-19: is there a link? BMJ Case Reports CP [Internet] 2020 [cited 2020 Nov 23]; 13 (8): e236419. Available from: https://casereports.bmj.com/content/13/8/e236419
4. Casos confirmados en Chile COVID-19 [Internet]. Ministerio de Salud – Gobierno de Chile [citado 22 de noviembre de 2020]. Disponible en: https://www.

minsal.cl/nuevo-coronavirus-2019-ncov/casos-confirmados-en-chile-covid-19/
5. Cea G, Jara P, Quevedo F. Características epidemiológicas del síndrome de Guillain-Barré en población chilena: estudio hospitalario en un período de 7 años. Rev Med Chile [Internet] 2015 [cited 2021 Jun 21]; 143 (2): 183-9. Available from: http://www.scielo.cl/scielo.php?script=sci_abstract&pid=S0034-98872015000200005&lng=es&nrm=iso&tlng=es
6. 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. Journal of Neurology [Internet] 2020 [cited 2020 Nov 23]. Available from: https://link.springer.com/epdf/10.1007/s00415-020-10124-x
7. Hahn AF. Guillain-Barré syndrome. The Lancet [Internet] 1998 [cited 2021 Jun 21]; 352 (9128): 635-41. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(97)12308-X/abstract
8. Abolmaali M, Heidari M, Zeinali M, Moghaddam P, Ramezani Ghamsari M, Jamshidi Makiani M, et al. Guillain-Barré syndrome as a parainfectious manifestation of SARS-CoV-2 infection: A case series. J Clin Neurosci. [Internet] 2021 [cited 2021 Mar 7]; 83: 119-22. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7666532/
9. Parra B, Lizarazo J, Jiménez-Arango JA, Zea-Vera AF, González-Manrique G, Vargas J, et al. Guillain–Barré Syndrome Associated with Zika Virus Infection in Colombia. New England Journal of Medicine [Internet]. 2016 [cited 2021 Jun 21]; 375 (16): 1513-23. Available from: https://doi.org/10.1056/NEJMoa1605564
10. Lantos JE, Strauss SB, Lin E. COVID-19-Associated Miller Fisher Syndrome: MRI Findings. American Journal of Neuroradiology [Internet] 2020 [cited 2021 Jun 21]; 41 (7): 1184-6. Available from: http://www.ajnr.org/content/41/7/1184
11. Doshi P. Covid-19: Do many people have pre-existing immunity? BMJ [Internet] 2020 [cited 2021 Mar 7]; 370: m3563. Available from: https://www.bmj.com/content/370/bmj.m3563
12. Frank CHM, Almeida TVR, Marques EA, de Sousa Monteiro Q, Feitoza PVS, Borba MGS, et al. Guillain-Barré Syndrome Associated with SARS-CoV-2 Infection in a Pediatric Patient. J Trop Pediatr. [Internet] 2020 [cited 2020 Nov 23]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7529009/
13. Keddie S, Pakpoor J, Mousele C, Pipis M, Machado PM, Foster M, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. Brain [Internet] 2021 [cited 2021 Jun 21]; 144 (2): 682-93. Available from: https://doi.org/10.1093/brain/awaa433
14. Leonhard SE, Mandarakas MR, Gondim FAA, Bateman K, Ferreira MLB, Cornblath DR, et al. Diagnosis and management of Guillain-Barré syndrome in ten steps. Nature Reviews Neurology [Internet]. 2019 [cited 2020 Nov 23]; 15 (11): 671-83. Available from: https://www.nature.com/articles/s41582-019-0250-9
15. Angoulvant F, Ouldali N, Yang DD, Filser M, Gajdos V, Rybak A, et al. Coronavirus Disease 2019 Pandemic: Impact Caused by School Closure and National Lockdown on Pediatric Visits and Admissions for Viral and Nonviral Infections-a Time Series Analysis. Clinical Infectious Diseases [Internet] 2021 [cited 2021 Mar 8]; 72 (2): 319-22. Available from: https://doi.org/10.1093/cid/ciaa710
16. Saint-Pierre Contreras G, Muñoz Gomez G, Silva Ojeda F. En búsqueda de otros virus respiratorios durante la pandemia COVID-19. Rev Clin Esp. [Internet] 2020 [cited 2021 Mar 8]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7604185/