Case report **UDC: 616.833-002:[616.98:578.834**
doi: 10.5633/amm.2023.0107

COMORBIDITY OF GUILLAIN-BARRE SYNDROME AND COVID-19 INFECTION: A CASE REPORT AND A REVIEW OF THE CURRENT LITERATURE

Radomir Damjanović[1,2], Aleksandar Stojanov[1,2], Ninoslava Simić[1,3], Andrija Jović[1,4], Dejan Popović[1,5]

Guillain-Barre syndrome is an immunologically mediated polyradiculoneuropathy characterized by a monophasic course, with a clinical peak within 4 weeks of disease onset. There have been several reports ofGuillain-Barré syndrome, related to COVID-19, days or weeks after the onset of respiratory symptoms. In contrast to that, we describe a case of acute sensorimotor demyelinating polyradiculoneuropathy, followed by COVID-19 infection. Our patient was successfully treated with intravenous immunoglobulins while COVID-19 was treated according to the latest clinical management protocol. In our case, neuropathy symptoms showed aparainfectious profile rather than a post-infectious one, which is uncommon inGuillain-Barré syndrome. *Acta Medica Medianae 2023;62(1):50-55.*

Key words: *Guillain-Barré syndrome (GBS), Coronavirus disease 2019 (COVID-19), weakness*

[1]University Clinical Center Niš, COVID hospital, Niš
[2]University Clinical Center Niš, Neurology Clinic, Niš,
[3] University Clinical Center Niš, Mental Health Protetction Center, Department for Child and Adolescent Psychiatry Niš, Serbia
[4] University Clinical Center Niš, Dermatovenerology Clinic, Niš, Serbia
[5] University Clinical Center Niš,Cardiovascular Deases Clinic, Niš, Srbija

Contact: Radomir Damjanović
48 Dr. Zoran Djindjića Blvd., 18000 Niš, Serbia
Tel: +381 61 44 86424
E-mail: rdamjanovic@gmail.com

Background

The World Health Organization declared the Coronavirus disease (COVID-19) pandemic on March 11, 2020, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). From then tonow, COVID-19 has aroused great interest of the scientific public all around the world, both due to the various presentations of the disease itself and due to the growing number of data about the connection of this respiratory infection with various organ systems (1). Although the most commonly described manifestations are mainly within the respiratory and gastrointestinal systems, COVID-19 may be associated with various neurological symptoms, such as headache, syncope, anosmia and ageusia (2, 3). Severe neurological diseases associated with COVID-19, including stroke, encephalopathies, encephalitis and immune neuropathies like Guillain-Barré syndrome (GBS) have also been reported (4, 5).

GBS is an immunologically mediated polyradiculoneuropathy characterized by a monophasic course, with a clinical peak within 4 weeks of disease onset (6). There have been several reports of GBS, related to COVID-19, days or weeks after onset of respiratory symptoms (7). In contrast to that, herein we present a patient with clinical symptoms characteristic for GBS, followed by COVID-19 infection.

Case presentation

A 36-year-old previously healthy man was admitted to the Clinic for Neurology at the University Clinical Center of Niš, Serbia, due to numbness of limbs, followed by weakness of lower limbs. The symptoms started while he was preparing for the job earlier that day. After a while, the patient also had weakness of his hands. On the admission, neurological examination showed the mild proximal weakness of upper and lower limbs, symmetrically reduced deep tendon reflexes of all four limbs and numbness of hands and foot. He had no comorbid conditions. There was no history of known respiratory or gastrointestinal infection, nor vaccination against COVID-19. According to the

protocol for admission of patients to our institution, an antigenic test for SARS Cov-2 was performed, which was negative. A standard set of biochemical analyzes was performed and elevated values of AST, ALT, and g-GT were marked off the findings. The blood count was of no clinical significance (Table 1). The next day, an MRI of the endocranium was performed and it showed reductive changes of the brain parenchyma as well as an MRI of the cervical spine,which was normal. Electrophysiological studies revealed acute sensorimotor demyelinating polyradiculoneuropathy, which, with albumin-cytologic dissociation (cerebrospinal fluid proteins 0.63 g/L) found at the cerebrospinal fluid examination, confirmed the diagnosis of GBS (Table 2).On the fourth day after admission, the patient had a fever (37.8°C) and cough, which indicated general biochemical analyzes to be performed (CRP 15 mg/L, AST 50 U/L, ALT 176 U/L, g-GT 70 U/L), as well as blood count (WBC 12.0 (10^9/L), NE 10.55 (10^9/L) (Table 1). X-ray of the chest showed inflammatory changes in the lower parts of the right and left lungs (Figure 1a).

Table 1. Oxygen saturation, haematological and biochemical parameters of our patient on admission, ICU admission and control analyses two weeks after onset of symptoms (the tenth day of treatment at the ICU).

	On admission	ICU admission	Control (10th day at the ICU)	Units and normal range
SpO2	97%	90%	98%	
WBC	8.7	15.8	18.6	Cells/L (4.0-9.0*10^9)
Lymphocytes	2.03	1.86	0.78	Cells/L (1.0-4.0*10^9)
Platelets	846	604	604	Cells/L (120-380*10^9)
RBC	5.02	4.81	4.20	Cells/L (4.30-5.80*10^12)
Hemoglobin	135	136	124	g/L (120-180)
Hematocrit	0.430	0.435	0.365	L/L (0.410-0.560)
CRP	8.9	138.2	31.8	mg/L (0.0-5.0)
GGT	55	78	164	U/L (0-55)
AST	35	42	135	U/L (10-37)
ALT	40	90	230	U/L (10-42)
Albumin	44	31	28	g/L (35-52)
D-dimer	230	704	560	ng/mL (<250)

Table 2. Motor nerve conduction studies on upper and lower extremities

Nerve	Distal latency (ms)	CMAP amplitude (mV)	Conduction Velocity (m/s)
Median, L	6.40	3.8	35.50
Ulnar, L	5.70	5.8	44.60
Median, R	7.20	3.7	37.40
Ulnar, R	5.50	5.4	40.10
Peroneal, L	12.75	1.2[a]	26.90
Tibial, L	Absent	Absent	Absent
Peroneal, R	11.50	1.3[a]	26.30
Tibial, R	Absent	Absent	Absent

a–temporal dispersion and conduction block

According to the indication of the Infectologist, a PCR test for SARS Cov-2 from a nasopharyngeal swab was done and found positive. The patient was transferred to the COVID-19 Department of the University ClinicalCenter in Niš, where he was connected to oxygen support (5L/min) due to oxygen saturation (SpO2) valueof90%. Further, there was a worsening of his neurologic symptoms reflected in examination findings of flaccid, areflexicquadriparesis, speech and swallowing difficulties.

The sixth day after admission, further deterioration
of respiratory function due to bulbar weakness occurred.

The patient was transferred to the Intensive Care Unit (ICU), intubated and connected to mechanical respiratory support (Mechanical ventilation–MV) with continuous analgesia with midazolam and remifentanil. Meanwhile, he was managed with five cycles of intravenous human immunoglobulins (0.6 g/kg/day). The value of C-reactive protein rose and blood count also worsened in terms of leukocytosis and neutrophilia.

On the twelfth day after admission, MV support (CPAP, FiO2 = 40%, SpO2 = 97%), with continuous infusion of remifentanil was resumed. He opened his eyes to the call and verbal contact was also possible.

Two days after (the fourteenth day after admission), the patient was disconnected from the MV, extubated and connected to oxygen support of 10L/min (SpO2 = 97%).

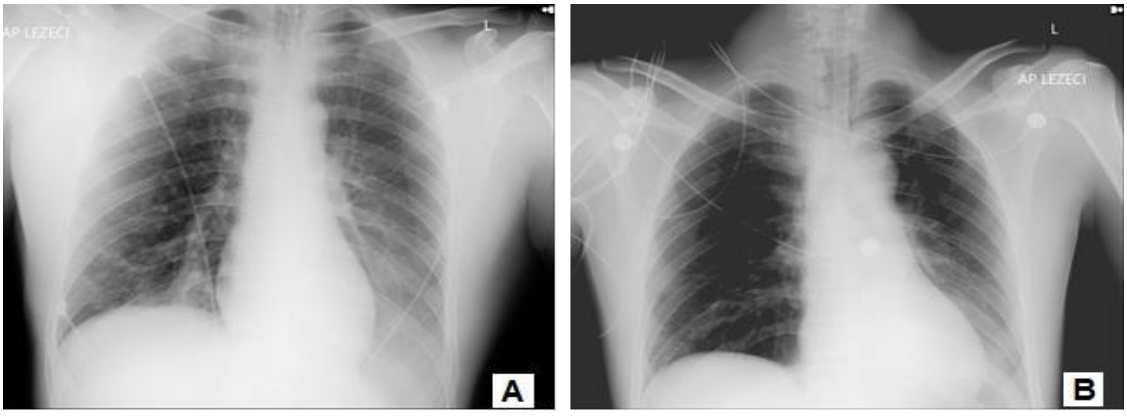

Figure 1. X-ray of the chest on the fourth day (A) and four weeks after admission (B)

On the twenty-first day after admission, the patient was in good general condition, with SpO2 = 98% and no oxygen support. He became SARS Cov-2 PCR negative, and the next day, he was discharged with a suggested physical rehabilitation program. Improvement of neurological findings was identified—mild quadriparesis with generally reduced muscle tendon reflexes and discrete bulbar symptomatology. During his hospitalization at the Covid-19 Department and Covid-19 Intensive Care Unit, the patient was treated according to the latest clinical management protocol for patients with Covid-19 infection (oxygen support, antiviral therapy, low molecular weight heparin, corticosteroid, gastroprotective and vitamin therapy). At the follow-up performed 30 days after discharge, the presented neurological examination showed difficulty with balance and coordination, while walking was possible only with support or mobility aid. Control chest X-ray four weeks after admission shows partial radiographic resolution of the lung opacities (Figure 1b).

Discussion and review of the literature

COVID-19 is caused by SARS-CoV-2, a single stranded RNA beta coronavirus. Numerous neurological manifestations have been associated with SARS-CoV-2 infection, such as acute cerebrovascular diseases, seizures, meningitis, encephalitis and skeletal muscle involvement (8,9). A study conducted in the Chinese population revealed that 36.4% of patients have some neurological symptoms during COVID-19 infection (10). There are case reports which describe GBS after COVID-19 infection or after vaccination against the SARS-CoV-2 virus (11 – 14). More accurately, GBS has been reported in less than 0.5% of SARS-CoV-2 infections (15). In this study, we reported a patient with GBS in which neurological symptoms (weakness, tingling and numbness of limbs, reduced deep tendon reflexes…) preceded symptoms of COVID-19 infection (fever, cough). Filosto et al. associated Covid-19 with the development of both postinfectious and parainfectious GBS (16). In our case, neuropathy symptoms showed a parainfectious profile rather than a postinfectious one, which is uncommon in GBS. Also, our patient does not have any history of an infection or vaccination a few weeks before the onset of symptoms. A review of the literature showed that the time from onset of the COVID-19 symptoms to the clinical GBS manifestations ranged between 3 and 28 days (in some patients, the onset of GBS preceded by a few days the first manifestations of COVID-19) (17). SARS-CoV-2 infection in its most severe form includes three stages: early infection, pneumonia and hyperinflammatory response (16). According to Siddiqi and Mehra, active viraemia occurs in the first two stages (18). Since the incubation period of SARS-CoV-2 is up to 14 days, it is difficult to determine at what stage GBS occurs. Searching through the literature, we found that neuropathy symptoms preceding Covid-19 were a rarity, although the parainfectous profile of GBS associated with COVID-19 was described in some papers (19, 20). Even in those papers in which neuropathy symptoms preceding COVID-19 symptoms,favourable outcome of GBSwas a rarity. A group of authors from the UK, interestingly, findno epidemiological or phenotypic clues of SARS-CoV-2 being causative of GBS, although they donot entirely rule out the possibility of that link (21). In addition, they have found that the intubation was more frequent in the Covid-19-related GBS, likely related to respiratory involvement. Our case (intubation on sixth day after admission), excellently depicts these findings.The same authors showed no significant homology of SARS-CoV-2 genetic or protein structure and human protein structures, which indicates that molecular mimicry is less likely. Mary et al. noted that posttranslational modification in viral capsid by the host cells could occur, which implicates the generation of immunogenic surface glicomolecules (22). We need more research to examine precisely this causal relationship. A group of authors from Canada described through a systematic review patients with GBS and concomitant Covid-19, following the Preferred reporting items for systematic reviews and meta-analysis statement (PRISMA) (23). They identified 1,450 records and 81 studies, and after applying exclusion criteria, a total number of patients was 99 cases, after PCR or serologic testing. A high level of diagnostic certainty for GBS (Brighton Criteria 1 or 2) fulfilled 77 patients. In those groups, the sensorimotor variant was reported in 64 cases, Miller-Fisher syndrome in 9, and other variants in the remainder. Authors marked male predominance (male to female ratio 2.5:1), which, according to previously reported risk factors for severe Covid-19 outcome, including increased age and male gender, could reflect the male predominance in this series of patients. AIDP was the most frequent electrophysiological profile in Covid-19-related GBS, which also expresses data reported by Dotes etal. (24). The treatment of GBS includes either IVIG or plasma exchange, despite still unclear mechanisms of their action (25). Although both treatment options have shown to be equally effective, a stronger effect could be obtained if treatment is administered within two weeks after disease onset (26–28).

Conclusion

Covid-19 is a multisystem disease that causes not only respiratory symptoms but also the neurologic ones. The concurrence of COVID-19 with GBS can increase the likelihood of neuromuscular respiratory failure, autonomic dysfunction, and other life-threatening symptoms. Given the growing number of reported cases of COVID-19-related GBS and its association with a severe disease course, it is important to emphasise the significance of early diagnosis and treatment of GBS in COVID-19 patients. In addition, no less effort should be made to elucidate the causal mechanism between the two diseases.

References

1. Gavriatopoulou M, Korompoki E, Fotiou D, Ntanasis-Stathopoulos I, Psaltopoulou T, Kastritis E, et al. Organ-specific manifestations of COVID-19 infection. Clin Exp Med 2020;20(4):493-506. [CrossRef][PubMed]
2. Suri V, Pandey S, Singh J, Jena A. Acute-onset chronic inflammatory demyelinating polyneuropathy after COVID-19 infection and subsequent ChAdOx1 nCoV-19 vaccination. BMJ Case Rep 2021;14(10):e245816. [CrossRef][PubMed]
3. Needham EJ, Chou SH, Coles AJ, Menon DK. Neurological implications of COVID-19 infections. Neurocrit Care 2020;32:667–671. [CrossRef][PubMed]
4. 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. [CrossRef][PubMed]
5. Caress JB, Castoro RJ, Simmons Z, Scelsa SN, Lewis RA, Ahlawat A, et al. COVID-19–associated Guillain-Barré syndrome: the early pandemic experience. Muscle Nerve 2020;62:485–91. [CrossRef][PubMed]
6. Van der Meché FG, Van Doorn PA, Meulstee J, Jennekens FG; GBS-consensus group of the Dutch Neuromuscular Research Support Centre. Diagnostic and classification criteria for the Guillain-Barré syndrome. Eur Neurol 2001;45:133–9. [CrossRef][PubMed]
7. Nepal G, Rehrig JH, Shrestha GS, Shing YK, Yadav JK, Ojha R, et al. Neurological manifestations of COVID-19: a systematic review. Crit Care 2020;24:421. [CrossRef][PubMed]
8. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77:683–9. [CrossRef][PubMed]
9. Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. Rev Neurol 2020;70:311–22. [CrossRef][PubMed]
10. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77(6):683–90. [CrossRef][PubMed]
11. Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: A case report. J Clin Neurosci 2020;76:233-235. [CrossRef][PubMed]
12. Hirayama T, Hongo Y, Kaida K, Kano O. Guillain-Barré syndrome after COVID-19 in Japan. BMJ Case Rep 2020;13(10):e239218. [CrossRef][PubMed]
13. Hasan T, Khan M, Khan F, Hamza G. Case of Guillain-Barré syndrome following COVID-19 vaccine. BMJ Case Rep 2021;14(6):e243629. [CrossRef][PubMed]
14. Bouattour N, Hdiji O, Sakka S, Fakhfakh E, Moalla K, Daoud S, et al. Guillain-Barré syndrome following the first dose of Pfizer-BioNTech COVID-19 vaccine: case report and review of reported cases. Neurol Sci 2022;43(2):755-761. [CrossRef][PubMed]
15. Guilmot A, Maldonado Slootjes S, Sellimi A, Bronchain M, Henseeuw B, Belkhir L, et al. Immune-mediated neurological syndromes in SARSCoV-2-infected patients. J Neurol 2021;268:751-7. [CrossRef][PubMed]
16. Filosto M, Cotti Piccinelli S, Gazzina S, Foresti C, Frigeni B, Servalli MC, et al. J Neurol Neurosurg Psychiatry 2021;92(7):751-756. [CrossRef][PubMed]
17. Zito A, Alfonsi E, Franciotta D, Todisco M, Gastaldi M, Cotta Ramusino M, et al. COVID-19 and Guillain-Barré Syndrome: A Case Report and Review of Literature. Front Neurol 2020;11:909. [CrossRef][PubMed]
18. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant 2020;39:405–7. [CrossRef][PubMed]
19. 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 2021;83:119-122. [CrossRef][PubMed]
20. Kajumba MM, Kolls BJ, Koltai DC, Kaddumukasa M, Kaddumukasa M, Laskowitz DT. COVID-19-Associated Guillain-Barre Syndrome: Atypical Para-infectious Profile, Symptom Overlap, and Increased Risk of Severe Neurological Complications. SN Compr Clin Med 2020;21:1-13. [CrossRef][PubMed]
21. Meyer Sauteur PM, Huizinga R, Tio-Gillen AP, Roodbol J, Hoogenboezem T, Jacobs E, et al. Mycoplasma pneumoniae triggering the Guillain-Barré syndrome: a case-control study. Ann Neurol 2016;80:566–80. [CrossRef][PubMed]
22. Mary B, Maurya S, Arumugam S, Kumar V, Jayandharan GR. Post-translational modifications in capsid proteins of recombinant adeno-associated virus (AAV) 1-rh10 serotypes. FEBS J 2019;286(24):4964-4981. [CrossRef][PubMed]
23. Aladawi M, Elfil M, Abu-Esheh B, Abu Jazar D, Armouti A, Bayoumi A, et al. Guillain Barre Syndrome as a Complication of COVID-19: A Systematic Review. Can J Neurol Sci 2022;49(1):38-48. [CrossRef][PubMed]
24. Kim JE, Heo JH, Kim HO, Song SH, Park SS, Park TH, et al. Neurological complications during treatment of middle east respiratory syndrome. J Clin Neurol 2017;13:227–33. [CrossRef][PubMed]
25. Kaeley N, Kabi A, Pillai A, Shankar T, Ameena S. Post-COVID-19 Guillain-Barré Syndrome: A Case Report With Literature Review. Cureus 2022;14(1):e21246. [CrossRef][PubMed]
26. Chevret S, Hughes RA, Annane D: Plasma exchange for Guillain-Barré syndrome. Cochrane Database Syst Rev 2017;2:CD001798. [CrossRef][PubMed]
27. Plasmapheresis and acute Guillain-Barré syndrome. The Guillain-Barré syndrome Study Group. Neurology 1985;35(8):1096-104. [CrossRef][PubMed]
28. Appropriate number of plasma exchanges in Guillain-Barré syndrome. The French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Ann Neurol 1997;41:298-306. [CrossRef][PubMed]

Pregledni rad **UDC: 616.833- 002:[616.98:578.834**
doi: 10.5633/amm.2023.0107

KOMORBIDITET SINDROMA GUILLAIN–BARRE I INFEKCIJE VIRUSOM COVID-19 – PRIKAZ SLUČAJA I PREGLED LITERATURE

Radomir Damjanović[1,2], Aleksandar Stojanov[1,2], Ninoslava Simić[1,3], Andrija Jović[1,4], Dejan Popović[1,5]

[1] Univerzitetski klinički centar Niš, COVID bolnica, Niš, Srbija
[2] Univerzitetski klinički centar Niš, Klinika za neurologiju, Niš, Srbija
[3] Univerzitetski klinički centar Niš, Centar za zaštitu mentalnog zdravlja, Departman za dečiju i adolescentsku psihijatriju, Niš, Srbija
[4] Univerzitetski klinički centar Niš, Klinika za dermatovenerologiju, Niš, Srbija
[5] Univerzitetski klinički centar Niš, Klinika za kardiovaskularne bolesti, Niš, Srbija

Kontakt: Radomir Damjanović
48 Dr. Zoran Djindjića Blvd., 18000 Niš, Serbia
Tel: +381 61 44 86424
E-mail: rdamjanovic@gmail.com

GBS je imunološki posredovana poliradikuloneuropatija koju karakteriše monofazni tok, a klinički pik dostiže unutar četiri nedelje od početka bolesti. Do sada je opisano nekoliko slučajeva GBS-a povezanog sa infekcijom izazvanom virusom COVID-19, nekoliko dana ili nedelja nakon početka respiratornih tegoba. Za razliku od toga, mi opisujemo slučaj akutne senzomotorne poliradikuloneuropatije, koja je praćena infekcijom izazvanom virusom COVID-19. Naš bolesnik uspešno je lečen intravenskim imunoglobulinima, dok je COVID-19 tretiran prema poslednjem kliničkom protokolu za lečenje bolesti izazvane ovim virusom. U ovom prikazu simptomi neuropatije imaju parainfektivni, a ne postinfektivni karakter, što je neuobičajeno za GBS. *Acta Medica Medianae 2023;62(1): 50-55.*

Ključne reči: *Guillain–Barré sindrom (GBS), COVID-19 virus, mišićna slabost*