Since December 2019, the world has been facing an outbreak of a new disease called coronavirus disease 2019 (COVID-19). The COVID-19 pandemic is caused by a novel beta-coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The SARS-CoV-2 infection mainly affects the respiratory system. Recently, there have been some reports of extra-respiratory symptoms such as neurological manifestations in COVID-19. According to the increasing reports of Guillain-Barré syndrome following COVID-19, we mainly focused on SARS-CoV-2 infection and Guillain-Barré syndrome in this review. We tried to explain the possibility of a relationship between SARS-CoV-2 infection and Guillain-Barré syndrome and potential pathogenic mechanisms based on current and past knowledge.

Keywords: Coronavirus, COVID-19, SARS-CoV-2, Neurological manifestations, Guillain-Barré syndrome

INTRODUCTION

Over the past two decades, coronaviruses have caused three epidemic diseases named the severe acute respiratory syndrome (SARS), the Middle East respiratory syndrome (MERS), and coronavirus disease 2019 (COVID-19) (1). All these three diseases are caused by coronaviruses belonging to the beta genus (2, 3). Infections caused by these beta-coronaviruses show a variable range of clinical manifestations, from being asymptomatic to severe disease and death (4). Although pulmonary symptoms are considered the main clinical manifestation, neurological complications associated with these three respiratory coronaviruses have also been reported (2, 5).

In this review, we mainly focused on SARS-CoV-2 infection and Guillain-Barré syndrome and tried to explain the potential pathogenic mechanisms based on current and past knowledge.
VIROLOGY OF SARS-COV-2

The coronavirus family consists of enveloped viruses with a positive single-stranded large RNA genome (6–8). Coronaviruses cause a wide variety of diseases in humans and some animals (9). Some of them have highly host-specific, while others are found on a range of hosts (10). According to genetic and serological properties, these viruses are divided into four subfamilies: α, β, γ, and δ, while the beta genus is also divided into four lineages of A, B, C, and D. Human coronavirus (HCoV) infections are caused only by alpha and beta genera (11, 12). Evidence indicated that the beta genus have more severe symptoms and complications compared to other genus (2). Besides, HCoVs are classified as zoonotic pathogens (13). Although these viruses cause respiratory infections in humans, their ability to affect other host organs such as heart, liver, gastrointestinal tract, kidney, Central and Peripheral Nervous System makes them complex pathogens (2, 5, 14–17).

In December 2019, the emerging virus causing COVID-19 was added to the coronavirus family. The virus, called SARS-CoV-2 belongs to the beta group, same as SARS-CoV and MERS-CoV, but to the lineage B (3). Analyses showed the SARS-CoV-2 is about 80% similar to the SARS-CoV. Both of these viruses enter the host cell by binding its surface spike protein to the host angiotensin converting enzyme-2 receptor (ACE-2). However, the binding affinity of the SARS-CoV-2 spike protein to the ACE-2 receptor is higher than that seen in SARS-CoV. Also it has recently been shown that SARS-CoV-2 may utilize basigin (BSG; CD147) and neuropilin-1 (NRP1) as binding receptors (18). Compared to SARS-CoV and MERS-CoV, the SARS-CoV-2 has higher transmissibility and pathogenicity (2, 3, 19–22).

During the current pandemic, most patients with COVID-19 show respiratory symptoms such as dry cough and shortness of breath. SARS-CoV-2 infection has clinical manifestations similar to those reported for SARS and MERS. Therefore, these three viruses are mainly known as respiratory pathogens. However, they could contribute to symptoms and complications related to other organs, especially in severe cases (2, 5, 23, 24). Gastrointestinal, cardiac, hepatic, kidney, ocular, cutaneous, and haematological, symptoms are the main extra-respiratory manifestations of patients with COVID-19 (8, 25–27). Recently, neurological symptoms were reported in some COVID-19 cases, raising concerns about the potential of the SARS-CoV-2 to invade nerves and lead to neurological complications, both in the acute and chronic phases. The term “neuro-COVID” is used to describe these complications (28, 29).

NEUROVIRULENCE OF HUMAN CORONAVIRUSES

The prevalence of neuro-COVID has been reported to vary between studies. Although the prevalence rate of neurological symptoms is estimated to be around 3.5 to 84% among COVID-19 patients, in most cases the SARS-CoV-2 RNA was not detected in the cerebrospinal fluid (CSF) (28, 30, 31). Among 58 patients with COVID-19 and neurological symptoms, the SARS-CoV-2 RNA was detected in CSF of 2 patients (3.4%). One patient with refractory headache and another with ADEM four days after the onset of COVID-19 symptoms (32). Also Domingues et al. detected SARS-CoV-2 in CSF using by RT-PCR and confirmed with deep sequenced. There was a 99.74 to 100% similarity between the patient virus to the worldwide sequences (33). On the other hand, organoids and in vivo studies in human ACE2 transgenic mice have demonstrated that the SARS-CoV-2 could infect neurons and contribute to cell death and neural damage. However, CSF and autopsy findings do not provide consistent support for direct CNS invasion. So SARS-CoV-2 related neurological symptoms may be the consequences of different mechanisms (18, 29, 34).

Given that coronaviruses could lead to short- or long-term neurological disorders, there was a hypothesis that these viruses may have neurovirulence because of the neurotropism and neuroinvasion of human coronaviruses (35–39). Since 2000, Arbour et al. found HCoV RNA in brain samples outside blood vessels, and affirmed the consistency of neuroinvasion by these respiratory pathogens in humans but considered the need of further studies to distinguish between opportunistic and disease-associated viral presence (40).

It seems that coronaviruses could be responsible for direct and indirect neurological symptoms and complications with central nervous system (CNS) (including headache, epileptic seizure, impaired consciousness and dizziness) and peripheral nervous system (PNS) manifestations (such as Guillain-Barré syndrome, anoxemia and neuralgia) (41), divided as para-infectious and post-infectious (5, 8, 23, 34, 42–45) (see Figure 1).

During the SARS-CoV and MERS-CoV outbreak, some neurological symptoms were among their other extra-pulmonary complications (Table 1). At the present SARS-CoV-2 outbreak, there have been increasing reports of clinical neurological disorders such as acute encephalomyelitis, acute flaccid paralysis (AFP), multiple sclerosis (MS), acute demyelinating encephalomyelitis (ADEM), and Guillain-Barré syndrome (GBS) as possible complications, supporting its neuroinvasion nature (12, 40, 51–53). Among them, Guillain-Barré Syndrome is the most frequent.

GUILLAIN-BARRÉ SYNDROME AND SARS-COV-2 INFECTION

Guillain-Barré syndrome is an acute acquired autoimmune disorder of the peripheral nerves that often occurs after

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; RNA, ribonucleic acid; HCoV, Human coronavirus; ACE-2, angiotensin converting enzyme-2 receptor; BSG, basigin; NRP1, neuropilin-1; CNS, central nervous system; PNS, peripheral nervous system; AF, acute flaccid paralysis; MS, multiple sclerosis; ADEM, acute demyelinating encephalomyelitis; GBS, Guillain-Barré syndrome; RT-PCR, reverse transcriptase PCR; PCR, polymerase chain reaction; CSF, cerebrospinal fluid; BBE, Bickerstaff’s encephalitis; CoVα, coronaviruses; IL, interleukin; TNF-α, tumor necrosis factor-alpha; CMV, cytomegalovirus; EBV, Epstein-Barr virus; arboviruses, arthropod-borne viruses; ZIKV, zika virus; HSP, heat shock proteins; IFN-γ, interferon-γ; MND, motor neuron diseases.
infection (54). In fact, GBS is symmetrical ascending paralysis, often caused by respiratory or gastrointestinal infections from a virus or bacteria (4). Many bacteria and viruses have been considered as possible trigger of GBS (55, 56). Before the recent pandemic, few cases of coronavirus associated to GBS were reported, but a systematic review pointed a significant increasing number of patients with GBS after the COVID-19 pandemic, with higher prevalence among older patients (mean age of 60 years) than with younger ones (mean age of 40 years) (57) (Table 2).

GBS associated to SARS-CoV-2 infection may follow the typical post-infectious pattern, with report indicating that it is also possible in children. GBS has also been reported as part of the “long COVID-19 syndrome” (69, 73). Nevertheless, there are also reports that GBS is a para-infectious paralysis associated with a viral infection (74). Almost all reported cases have acute onset within a few days of onset of viral infection (75) (see Figure 2).

Possible Mechanisms of Guillain-Barré Syndrome Involving Virus and Bacteria

Molecular mimicry between microbial and neural antigens is a major driving force in this disorder. The interaction between microbial agents and the host that dictates the immune response to the unwanted auto reactivity is not well understood yet. On the other hand, most people (>99%) who are exposed to immune stimulus, as a result of GBS-associated infection do not develop unwanted autoimmunity. It seems that genetics and environmental factors affect the susceptibility of individual to this disease (56, 76, 77).

The association of various microorganisms with Guillain-Barré syndrome has been reported such as Campylobacter jejuni (C. jejuni), Mycoplasma pneumoniae, Haemophilus influenza, Cytomegalovirus (CMV), Epstein-Barr virus (EBV), influenza A, varicella-zoster, hepatitis (A, B and E), Zika and Chikungunya viruses (78–91). C. jejuni has been identified as the most common pathogen causing this disorder (91, 92).

In 2001, Yuki showed that the core lipo-oligosaccharides of the Campylobacter jejuni strains associated with GBS have structural similarities to various gangliosides in peripheral nerve membranes, suggesting that molecular mimicry of gangliosides may contribute to GBS (93). Molecular mimicry of gangliosides in C. jejuni results in the production of anti-ganglioside antibodies that bind to gangliosides in the axonal membrane at the Ranvier node. Activation of complement leads to disruption of voltage-gated sodium channels, disruption of nodal structure, and formation of the membrane attack complex that leads to calcium influx. Eventually, these changes cause axonal damage and attract macrophages, which could then migrate between axon and myelin (80, 94). Guillain-Barré-associated viral infections show similar mechanisms to bacterial GBS. However, due to the wide range of viral antigens that may be associated with GBS, the pathophysiology, the clinical course, and outcomes may vary (78).
Studies have described the role of GM2 anti-glycoside antibodies in the pathogenesis of CMV-related GBS. The findings of these studies showed that anti-GM2 IgM antibodies are induced in acute cytomegalovirus infection through molecular mimicry between GM2 and the antigens induced by CMV infection (77, 93, 95, 96). For hepatitis A, B, C, or E, a possible molecular mimicry of gangliosides (97). In addition, there are other alternative mechanisms described for Zika-related GBS. It could be due to a direct viral neuropathic effect, and cross-reactive antibodies formed during previous infections with a detrimental effect on nerve function. The underlying mechanisms of para-infectious pathogenesis have not yet been identified. It has been suggested that specific Zika virus-peptides may not only cross-react but also induce a cellular
immune response via antigen-presenting cell activation of T-lymphocytes (104, 106, 108, 109).

During the recent pandemic, there is also growing evidence that SARS-CoV-2 infection is associated with immune-mediated neurological complications, for example, in the form of GBS (65, 110). The exact pathogenesis of COVID-19-related neurological damage is still largely unknown. Considering that previous viral outbreaks, molecular mimicry between SARS-CoV-2 and various human organs and tissues have been hypothesized as a potential trigger of multi-organ autoimmunity in COVID-19 (104, 111–114). Moreover, failure to detect the SARS-CoV-2 in most of the CSF patient samples supports an immune mechanism rather than direct invasion (18).

In a recent study by Lucchese and Flöel, sequence analysis of the 41 human proteins associated with acute and chronic immune-mediated neuropathies revealed that SARS-CoV-2 contained two immunologically-related hexapeptides (KDKKKK in nucleocapsid and EIPKEE in Orf1ab) with the human heat shock proteins 90 (HSP90B and HSP90B2) and 60 (HSP60), respectively (113). These authors hypothesized that SARS-CoV-2 infection may trigger an adaptive immune response in which T cell-B cell interactions result in the production specific antibodies similar to ganglioside-peptide sequences or structure, resulting in loss of self-tolerance (113). The gangliosides located on the membranes of neurons and the Schwann-cells, which form the myelin sheath, act as receptors for antiganglioside antibodies, promoting neutralization of neurons complement inhibitory activity, which turn them into targets for autoimmune-mediated destruction of myelin sheaths or axons (113).

About 50 to 85% of previously reported cases with GBS or its variants have anti-ganglioside antibodies in their serum. However, there are limited data on the presence of anti-ganglioside antibodies in the patients with COVID-19 related GBS. Studies have not reported increase in the serum titers of anti-ganglioside antibodies in GBS patients with COVID-19. Recently, Dufour et al. reported first case with COVID-19 related GBS with positive GM1 antibody (67, 75). Therefore, further studies are necessary to confirm the presence of anti-ganglioside antibodies in COVID-19 related GBS.

This molecular mimicry has also been shown in the implication of HSPs in some immune-mediated clinical conditions (115). A 2015 study by Loshaj-Shala et al. reported a high homology between C. jejuni DnaK and GroEL with the human peripheral nerve HSP70 and HSP60, respectively (92). These results strongly support the potential role of chaperone molecules in the progression of the autoimmune response related to GBS (92). Also an etiological relationship between some neurological diseases and autoantibodies against HSP family proteins has sometimes been described (116, 117). It is noteworthy that autoantibodies targeting different families of HSPs were increased in serum and CSF of patients with GBS compared to healthy controls (118, 119). In a study, Yonekura et al. demonstrated that IgG and IgM antibody titers against several HSPs (including
ACKNOWLEDGMENTS

The authors would like to acknowledge the support from the Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences.

REFERENCES

1. De Wit E, Van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: Recent Insights Into Emerging Coronaviruses. Nat Rev Microbiol (2016) 14:523–34. doi: 10.1038/nrmicro.2016.81
2. Harb JG, Noureldine HA, Chedid G, Eldine MN, Abdallah DA, Chedid NF, et al. SARS, MERS and COVID-19: Clinical Manifestations and Organ-System Complications: A Mini Review. Pathog Dis (2020) 78:1–7. doi: 10.1093/femsdp/ftaa033
3. Wang L, Wang Y, Ye D, Liu Q. Review of the 2019 Novel Coronavirus (SARS-CoV-2) Based on Current Evidence. Int J Antimicrob Agents (2020) 55:105948. doi: 10.1016/j.ijantimicag.2020.105948
4. Bridwell R, Long B, Gottlieb M. Neurologic Complications of COVID-19. Am J Emerg Med (2020) 38:1549.e3–e7. doi: 10.1016/j.ajem.2020.05.024
5. Kwong KCNK, Mehta PR, Shukla G, Mehta AR. COVID-19, SARS and MERS: A Neurological Perspective. J Clin Neurosci (2020) 77:13–6. doi: 10.1016/j.jocn.2020.04.124
6. He F, Deng Y, Li W. Coronavirus Disease 2019: What We Know? J Med Virol (2020) 92:719–25. doi: 10.1002/jmv.25766
7. Sahin AR. 2019 Novel Coronavirus (COVID-19) Outbreak: A Review of the Current Literature. Eurasian J Med Oncol (2020) 4:1–7. doi: 10.14744/ ejmo.2020.12220
8. Nordvig AS, Rimmer KT, Willey JZ, Thakur KT, Boehme AK, Vargas WS, et al. Potential Neurological Manifestations of COVID-19. Neurol Clin Pract (2020) 11(2):e135–46. doi: 10.1212/CPJ.0000000000000897
9. Fehr AR, Perlman S. Coronaviruses: An Overview of Their Replication and Pathogenesis. Coronavirus: Methods Protocols: Springer (2015) 1282. doi: 10.1007/978-1-4939-2438-7_1
53. Sharma K, Tengsupadk S, Sanchez O, Phaltas R, Maertens P. Guillain–Barré Syndrome With Unilateral Peripheral Facial and Bulbar Palsy in a Child: A Case Report. SAGE Open Med Case Rep (2019) 7:1–2. doi: 10.1177/2050313X18038756

54. Yamana M, Kuwahara M, Fukumoto Y, Yoshikawa K, Takada K, Kusunoki S. Guillain-Barré Syndrome and Related Diseases After Influenza Virus Infection. Neuro Immunol Neuroinflamm (2019) 6:1–7. doi: 10.1210/NNIN.0000000000000575

55. Berciano J, Orizaola P, Gallardo E, Pelayo-Negro AL, Sanchez-Juan P, Infante J, et al. Very Early Guillain-Barré Syndrome: A Clinical-Electrophysiological and Ultrasonographic Study. Clin Neurophysiol Pract (2020) 5:1–9. doi: 10.1016/j.cnp.2019.11.003

56. Iasti AK, Selmi C, Sarmiento-Monroy JC, Vega DA, Anaya JM, Gershwin ME. Guillain-Barré Syndrome: Causes, Immunopathogenic Mechanisms and Treatment. Expert Rev Clin Immunol (2016) 12:1175–89. doi: 10.1080/1744666X.2016.1193006

57. Gittammer LMT, Feris SNV. Giacomano AvO. Relation Between COVID-19 and Guillain-Barré Syndrome in Adults: A Systematic Review. Neurology (English Edition) (2020) 35:646–54. doi: 10.1016/j.nrleng.2020.07.005

58. 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 (Korea) (2017) 13:123–37. doi: 10.3988/jcn.2017.13.3.227

59. Coen M, Jeansonc G, Almeidad LAC, Hübers A, Stierlin F, Najjar I, et al.COVID-19 may Induce Guillain-Barré Syndrome Related to COVID-19 Infection. E. COVID-19 may Induce Guillain-Barré Syndrome Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Detection and Coronavirus Disease 2019 in a Child. J Pediatr Infect Dis Soc (2020) 15:547–60. doi: 10.1093/jpids/piaa086

60. Alberti P, Beretta S, Piatti M, Karantzoulis A, Piatti ML, Santoro P, et al. Guillain-Barré Syndrome: Causes, Immunopathogenic Mechanisms and Treatment. Expert Rev Clin Immunol (2016) 12:1175–89. doi: 10.1080/1744666X.2016.1193006

61. Sedaghat Z, Karimi N. Guillain-Barré Syndrome Associated With COVID-19 Infection: A Case Report. J Clin Neurol (2020) 76:233–5. doi: 10.1016/j.jocn.2020.04.062

62. Padroni M, Mastrangelo V, Asioli GM, Pavolucci L, Abu-Rumeileh S, Padroni M, et al. Guillain-Barré Syndrome Following Varicella-Zoster Virus Infection. Eur J Clin Microbiol Infect Dis (2019) 38:87–91. doi: 10.1007/s10096-018-3399-5

63. Khalifa M, Zakaria F, Ragab Y, Saad A, Bamaga A, Emad Y, et al. Guillain-Barré Syndrome Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Detection and Coronavirus Disease 2019 in a Child. J Pediatr Infect Dis Soc (2020) 9(4):510–3. doi: 10.1016/j.jpids.2020.04.086

64. Islam B, Islam Z, GeurtsvanKessel CH, Jahan I, Endtz HP, Mohammad QD, et al. Guillain-Barré Syndrome Following Varicella-Zoster Virus Infection. Eur J Clin Microbiol Infect Dis (2018) 37:1175–81. doi: 10.1007/s10096-018-3399-5

65. Goodfellow JA, Willison HJ. Guillain-Barré Syndrome: A Century of Progress. Nat Rev Neurol (2016) 12:723–31. doi: 10.1038/nrneurol.2016.172

66. Ray G, Ghosh B, Bhattacharyya R. Acute Hepatitis B Presenting as Guillain-Barré Syndrome. Indian J Gastroenterol (2020) 41:1351–5. doi: 10.1086/594124

67. Mardani M, Khodashahi R, Faghani Y. Guillain-Barré Syndrome Associated With SARS-CoV-2 Infection. Clin J Gastroenterol (2018) 11:317–21. doi: 10.1067/mjg.2018.132838

68. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain-Barré Syndrome Following SARS-CoV-2 Infection: Part of ‘Long COVID-19 Syndrome’? BMJ Case Rep (2021) 14(5):e202109431. doi: 10.1136/bcr-2021-202109431

69. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré Syndrome Associated With SARS-CoV-2 Infection: Causality or Coincidence? Lancet Neurol (2020) 19:383–4. doi: 10.1016/S1474-4422(20)30109-5

70. Ottaviani D, Bosio F, Tranquilli E, Gapieni I, Pedrotti G, Cozzo S, et al. Very Early Guillain-Barré Syndrome in Coronavirus Disease 2019 (COVID-19): A Case Report From an Italian COVID-Hospital. Neurol Sci (2020) 41:351–4. doi: 10.1007/s10072-020-04488-8

71. Bastug A, Bektas H, Buyuktarakci C, Bodur H. Parainfectious Guillain-Barré Syndrome in a Patient Diagnosed With COVID-19. Res Square (2021). doi: 10.21203/rs.3.rs.215097/v1

72. Sivadon-Tardy V, Orlikowski D, Porcher R, Sharshar T, Durand MC, Enouf V, et al. Guillain-Barré Syndrome and Influenza Virus Infection. Clin Infect Dis (2009) 48:48–56. doi: 10.1086/594124

73. Steininger C, Seiser A, Gueler N, Puchhammer-Stickl F, Abele SW, Stanek G, et al. Primary Cytomegalovirus Infection in Patients With Guillain-Barré Syndrome. J Neuroimmunol (2007) 183:214–9. doi: 10.1016/j.jneumim.2006.11.006

74. Kennedy M, Apostolova L. A Rare Case of Infectious Mononucleosis Complicated by Guillain-Barré Syndrome. Neurol Int (2013) 5:20–2. doi: 10.4081/ni.2013.e7

75. Van Der Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, Van Doorn PA. Guillain-Barré Syndrome: Pathogenesis, Diagnosis, Treatment and Prognosis. Nat Rev Neurol (2014) 10:469–82. doi: 10.1038/nrneurol.2014.121

76. Loshaj-Shala A, Regazzoni L, Daci A, Orioli M, Brezovska K, Panovska AP, et al. Guillain-Barré Syndrome (GBS): New Insights in the Molecular Mimicry Between C. Jejuni and Human Peripheral Nerve (HPN) Proteins. J Neuroimmunol (2015) 289:168–76. doi: 10.1016/j.jneuroim.2015.11.005

77. Yuki N, Infectious Origins of, and Molecular Mimicry in Guillain-Barré and Fisher Syndromes. Lancet Infect Dis (2001) 1:29–37. doi: 10.1016/S1473-3099(01)00119-6

78. Susuki K, Rasband MN, Tohyama K, Koibuchi K, Okamoto S, Funakoshi K, et al. Anti-GM1 Antibodies Cause Complement-Mediated Disruption of
