Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Autoimmunity Reviews 19 (2020) 102681

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Guillain Barré syndrome and COVID-19: Possible role of the cytokine storm

Dear Editor

The rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in the global pandemic of coronavirus disease 2019 (COVID-19). A member of the β-coronavirus family, the SARS-CoV-2 predominantly targets the angiotensin-converting enzyme 2 (ACE2) receptor protein [1]. The receptor is expressed on a variety of cell types, including vascular and respiratory epithelium and alveolar monocytes. The SARS-CoV-2 augments a severe acute immune-response with a marked upsurge of pro-inflammatory cytokines, also known as the *cytokine release storm (CRS)*, which is instrumental to the pathogenesis of COVID-19 [2]. Although the most serious manifestations of COVID-19 are pulmonary and neurological, both central and peripheral complications have been reported in 36% cases [3]. Several reports have described COVID-19 associated Guillain-Barré Syndrome (GBS) [4–6]. GBS can be associated with considerable morbidity and mortality due to rapidly progressive weakness of bulbar, limb and respiratory muscles [4–7]. Herein, we briefly explore the role of COVID-19-mediated CRS, its possible association with GBS and therapeutic implications.

GBS is a heterogeneous disease with considerable clinical and phenotypic variation. The two major types include acute inflammatory demyelinating polyneuropathy (AIDP - demyelinating) and acute motor axonal neuropathy (AMAN-axonal), where the immunologic processes target the myelin or the axons, respectively. In about 2/3rd of cases, GBS is preceded by a bacterial or viral infection of the respiratory or gastrointestinal tract with Campylobacter jejuni (26–65%) [8], cytomegalovirus (10–15%), Epstein–Barr virus (8–10%) being the most common pathogen. Other agents include mycoplasma pneumonia, *Haemophilus influenzae*, and influenza A virus [9]. Antecedent infection with hepatitis E virus has been identified as a potential trigger of GBS in up to 5 to10% patients [10,11]. Further, previous outbreaks of the Zika virus resulted in an upsurge in the incidence of GBS that was more severe [12]. About 50–85% of patients with GBS or its variants have antiganglioside antibodies in their sera [13,14]. Gangliosides are sialylated glycosphingolipids found abundantly in various nervous tissues and the antibodies develop post-infection due to shared epitopes between the gangliosides and the infectious agent. In GBS, this phenomenon of molecular mimicry leads to binding of the antibody to nerves causing impaired conduction of impulses and axonal degeneration.

Recent reports show that GBS associated with COVID −19 has multiple distinctive features. As compared to the typical "*post-infectious*" course in the classical form, the GBS associated with COVID-19 presents as an "*acute para-infection*" as almost all reported cases have had acute onset within days of onset of viral infection, mostly within the first few days. The disease typically follows a florid course leading to flaccid limb paralysis and respiratory failure requiring ventilatory support within days of onset. Both axonal and demyelinating variants have been reported, more so the former. In all cases, the cerebrospinal fluid (CSF) shows elevated protein levels with few inflammatory cells. The CSF PCR essay for COVID −19 virus has consistently been negative and MRI, when done, did not show enhancement of the nerve roots in many cases. Importantly, no reported patients showed rise in the serum titers of antiganglioside antibodies. Finally, therapeutic response to conventional therapies, both intravenous immunoglobulin (IVIg) or plasma exchange, in the GBS associated with COVID-19 has been suboptimal with outcomes being worse as compared to classical GBS.

The differences in COVID-19 associated GBS with GBS in the classical form are intriguing. Direct damage to the nerve roots by the COVID-19 virus, as seen with CMV and VZV infections, appears unlikely as the CSF lacks signs of infection, the CSF PCR is negative for the COVID −19 virus and the nerve root involvement is not always obvious on MRI. More likely the nerves/nerve roots are affected as part of systemic, acute, and severe dysimmune processes in association with widespread pulmonary and extra-pulmonary manifestations of COVID-19. This has been previously noted with Zika virus infection where the GBS occurs early during the course of the infective process and has a more rapid and severe course with distal demyelination of the nerves [15].

In COVID-19, the early CRS results in a surge of several cytokines including interleukin-1β (IL-1β), IL-6, IL-17, tumor necrosis factor-α (TNF- α), interferon-γ (IFN-γ) along with other chemokines [16], which are mediators of the widespread and severe damage culminating in multi-organ failure and death primarily associated with acute respiratory distress syndrome [17]. Many of the same cytokines have been implicated in the pathogenesis of classical GBS (*see below*) and it is likely that the early CRS in COVID-19 plays a pivotal role in the concurrent development of GBS and its rapid progression. This notion is further supported by the following known observations:

1. In experimental models of GBS i.e. experimental autoimmune neuritis (EAN) administration of recombinant IFN-γ has shown to worsen the condition, administration of a monoclonal antibody to IFN-γ suppresses the disease, and IFN-γ receptor deficient mice show milder disease than wild type [18].
2. Allelic polymorphism of TNF-α, crucial in macrophage signaling and Th1 pathway, is associated with AMAN susceptibility and possibly involved in GBS pathogenesis. Furthermore, it is endorsed by the elevated levels of TNF- α during the acute phase of GBS
3. Serum TNF-α levels are elevated during the acute phase of GBS, correlate with its clinical severity and decrease after treatment with IVIg or plasma exchange [18].
4. CSF levels of IFN-γ, IL-4, IL-17, and IL-22 are elevated in GBS [19,20]. IL-17 is implicated in myelin damage via Schwann cell mediated demyelination [21]. More importantly the CSF levels of both IL-17 and IL-22 correlate with severity of GBS on disability scale scores [22].

https://doi.org/10.1016/j.autrev.2020.102681
Received 3 August 2020; Accepted 10 August 2020
Available online 22 October 2020

5. The Th1 and Th17-related cytokine levels in the blood, are significantly increased in GBS patients and the number of circulating Th17 cells and level of IL-17A decrease after treatment with IVIg [20].
6. The COVID-19-mediated CRS causes a surge in the brain of IL-2, IL-7, IFN-γ, macrophage inflammatory protein 1-α, and TNF-α, leading to hyperinflammation, severe encephalopathy and stroke [23].

These observations have important clinical implications for treatment of COVID-19 associated GBS, particularly during the early phase. Patients presenting with the typical GBS and its variants respond favorably to IVIg and plasma exchange but not to corticosteroids. However, in the case of GBS associated with COVID-19, and its possible association with CRS, the role of steroids has not been determined. Indeed, corticosteroids are reported to be effective in the management of the pulmonary and extra-pulmonary manifestations of COVID-19, if used early in the course of the disease [24]. Likely, this is due to their ability to modulate a number of cytokines i.e. IL-1, IL-6, IL-8, IL-12 and TNFα. Low dose corticosteroids have also been used previously, in the closely related SARS-CoV outbreaks [25,26]. Untill more data becomes available in patients with COVID-19 associated GBS, it may be prudent to keep concurrent steroids on board along with other conventional therapies.

Declaration of Competing Interest

None.

Acknowledgment

F.S.H. has been funded by Mitacs *Accelerate*. M.A.E is a Parkinson Canada Scholar.

References

[1] Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395 (10224):565–74. https://doi.org/10.1016/S0140-6736(20)30251-8.
[2] Cao W, Li T. COVID-19: towards understanding of pathogenesis. Cell Res 2020;30: 367–9. https://doi.org/10.1038/s41422-020-0327-4.
[3] Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77(6):683–90. https://doi.org/10.1001/jamaneurol.2020.1127.
[4] Ottaviani D, Boso F, Tranquillini E, et al. Early Guillain-Barré syndrome in coronavirus disease 2019 (COVID-19): a case report from an Italian COVID-hospital. Neurol Sci 2020;41:1351–4. https://doi.org/10.1007/s10072-020-04449-8.
[5] Farzi MA, Ayromlou H, Jahanbakhsh N, Bavil PH, Janzadeh A, Shayan FK. Guillain-Barré syndrome in a patient infected with SARS-CoV-2, a case report. J Neuroimmunol 2020;346:577294. https://doi.org/10.1016/j.jneuroim.2020.577294.
[6] Bigaut K, Mallaret M, Baloglu S, et al. Guillain-Barré syndrome related to SARS-CoV-2 infection. Neurol Neuroimmunol Neuroinflamm 2020;7:785. https://doi.org/10.1212/NXI.0000000000000785.
[7] Toscano G, Palmerina F, Ravaglia S, et al. Guillain-Barré syndrome associated with SARS-CoV-2. N Engl J Med 2020;382(26):2574–6. https://doi.org/10.1056/NEJMc2009191.
[8] Kuwabara S, Yuki N. Axonal Guillain-Barré syndrome: concepts and controversies. Lancet Neurol 2013;12(12):1180–8. https://doi.org/10.1016/S1474-4422(13)70215-1.
[9] Hartung H-P. Infections and the Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 1999;66:277. https://doi.org/10.1136/jnnp.66.3.277.
[10] van Den Berg B, van Der Eijk AA, Pas SD, et al. Guillain-Barré syndrome associated with preceding hepatitis E virus infection. Neurology 2014;82(6):491–7. https://doi.org/10.1212/WNL.0000000000000111.
[11] Geurtsvankessel CH, Islam Z, Mohammad QD, Jacobs BC, Endtz HP, Osterhaus ADME. Hepatitis E and Guillain-Barré syndrome. Clin Infect Dis 2013; 57:1369–70. https://doi.org/10.1093/cid/cit512.
[12] Dirlikov E, Major CG, Medina NA, et al. Clinical features of Guillain-Barré syndrome with vs without zika virus infection, Puerto Rico, 2016. JAMA Neurol 2018; 75(9):1089–97. https://doi.org/10.1001/jamaneurol.2018.1058.
[13] Wanleenuwat P, Iwanowski P, Kozubski W. Antiganglioside antibodies in neurological diseases. J Neurol Sci 2020;408:116576. https://doi.org/10.1016/j.jns.2019.116576.
[14] Koga M, Yuki N, Hirata K. Antiganglioside antibody in patients with Guillain-Barré syndrome who show bulbar palsy as an initial symptom. J Neurol Neurosurg Psychiatry 1999;66:513–6. https://doi.org/10.1136/jnnp.66.4.513.
[15] Uncini A, Shahrizaila N, Kuwabara S. Zika virus infection and Guillain-Barré syndrome: a review focused on clinical and electrophysiological subtypes. J Neurol Neurosurg Psychiatry 2017;88:266–71. https://doi.org/10.1136/jnnp-2016-314310.
[16] Jamilloux Y, Henry T, Belot A, et al. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. Autoimmun Rev 2020;19(17):102567. https://doi.org/10.1016/j.autrev.2020.102567.
[17] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46(5):846–8. https://doi.org/10.1007/s00134-020-05991-x.
[18] Zhang HL, Zheng XY, Zhu J. Th1/Th2/Th17/Treg cytokines in Guillain-Barré syndrome and experimental autoimmune neuritis. Cytokine Growth Factor Rev 2013;24(5):443–53. https://doi.org/10.1016/j.cytogfr.2013.05.005.
[19] Hohnoki K, Inoue A, Koh CS. Elevated serum levels of IFN-γ, IL-4 and TNF-α/unelevated serum levels of IL-10 in patients with demyelinating diseases during the acute stage. J Neuroimmunol 1998;87(1–2):27–32. https://doi.org/10.1016/S0165-5728(98)00053-8.
[20] Li S, Yu M, Li H, Zhang H, Jiang Y. IL-17 and IL-22 in cerebrospinal fluid and plasma are elevated in Guillain-Barré syndrome. Mediators Inflamm 2012;2012: 260473. https://doi.org/10.1155/2012/260473.
[21] Stettner M, Lohmann B, Wolffram K, et al. Interleukin-17 impedes schwann cell-mediated myelination. J Neuroinflammation 2014;11:63. https://doi.org/10.1186/1742-2094-11-63.
[22] Maddur MS, Rabin M, Hegde P, et al. Intravenous immunoglobulin exerts reciprocal regulation of Th1/Th17 cells and regulatory T cells in Guillain-Barré syndrome patients. Immunol Res 2014;60:320–9. https://doi.org/10.1007/s12026-014-8580-6.
[23] Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020;87:18–22. https://doi.org/10.1016/j.bbi.2020.03.031.
[24] Russell B, Moss C, George G, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. Ecancermedicalscience 2020;14:1022. https://doi.org/10.3332/ecancer.2020.1022.
[25] Chihrin S, Loutfy MR. Overview of antiviral and anti-inflammatory treatment for severe acute respiratory syndrome. Expert Rev Anti Infect Ther 2005;3(2):251–62. https://doi.org/10.1586/14787210.3.2.251.
[26] Lam CWK, Chan MHM, Wong CK. Severe acute respiratory syndrome: clinical and laboratory manifestations. Clin Biochem Rev 2004;25:121–32.

Faraz S. Hussain[a], Mohamed A. Eldeeb[b,*], Derrick Blackmore[a], Zaeem A. Siddiqi[a,*]

[a] *Division of Neurology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada*

[b] *Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada*

[*] Corresponding authors.
E-mail addresses: eldeeb@ualberta.ca (M.A. Eldeeb), zsiddiqi@ualberta.ca (Z.A. Siddiqi).