Review
Neurologic Complications in Adult and Pediatric Patients with SARS-CoV-2 Infection

Kendall Howard 1,2, Taylor Williams 2, Elizabeth Fitch 2, Heather Ots 2, Esther Pototskiy 1, Jay Hawkshead 3, Zelda Ghersin 4 and Alberto E. Musto 1,5,*

1 Department of Pathology and Anatomy, Eastern Virginia Medical School, Norfolk, VA 23507, USA; howardk@evms.edu (K.H.); pototsev@Evms.edu (E.P.)
2 School of Medicine Program, Eastern Virginia Medical School, Norfolk, VA 23507, USA; williatc@evms.edu (T.W.); fitche@evms.edu (E.F.); otshd@evms.edu (H.O.)
3 Virginia Department of Corrections Health Services Unit, Richmond, VA 23225, USA; jhawksh@tulane.edu
4 Pediatric Intensive Care Unit, Hackensack Meridian K. Hovnanian Children’s Hospital Hackensack Meridian School of Medicine, Neptune, NJ 07753, USA; zelda.ghersin@hmhn.org
5 Department of Neurology, Eastern Virginia Medical School, Norfolk, VA 23507, USA
* Correspondence: mustoae@evms.edu

Abstract: SARS-CoV-2 has an impact on the nervous system as a result of pathological cellular and molecular events at the level of vascular and neural tissue. Severe neurologic manifestations including stroke, ataxia, seizure, and depressed level of consciousness are prevalent in patients with SARS-CoV-2 infection. Although the mechanism is still unclear, SARS-CoV-2 has been associated with the pathogenesis of intravascular coagulation and angiotensin-converting enzyme-I, both exacerbating systemic inflammation and contributing to hypercoagulation or blood–brain barrier leakage, resulting in ischemic or hemorrhagic stroke. On the other hand, the SARS-CoV-2 spike protein in neural tissue and within the cerebrospinal fluid may induce neural dysfunction, resulting in neuroinflammation, which is exacerbated by peripheral and neural hypercytokinemia that can lead to neuronal damage and subsequent neuroinflammation. A deeper understanding of the fundamental biological mechanisms of neurologic manifestations in SARS-CoV-2 infection can pave the way to identifying a single biomarker or network of biomarkers to help target neuroprotective therapy in patients at risk for developing neurological complications.

Keywords: neuroinflammation; COVID-19; epilepsy; epileptiform abnormalities

1. Introduction
While society is still grappling with the acute effects of the COVID-19 pandemic, the long-term sequelae from the illness remain largely unknown. Aside from the predominant respiratory manifestations that have been hallmarks of serious disease, severe acute respiratory syndrome coronaviruses (SARS-CoV-1 and SARS-CoV-2) have been implicated in a range of severe neurologic complications, including acute ischemic or hemorrhagic stroke [1–6], encephalopathy [7–11], encephalitis [12,13], epilepsy/seizures [14,15], acute transverse myelitis [16–18], and Guillain–Barre syndrome (GBS) [19,20]. While non-life-threatening complications such as myalgia and ageusia affect 22% and 20% of patients, respectively, more severe complications such as encephalopathy and acute cerebrovascular disease are estimated to be seen in 2.5% to 10% of patients. Case reports from the United Kingdom of 143 patients with neurological symptoms revealed that 32% developed altered mental statuses, and almost 50% required intensive level care [21]. In the pediatric population, a multicenter study of children hospitalized with either acute COVID-19 or multi-system inflammatory syndrome in children (MIS-C) documented 22% of pediatric cases with neurological involvement, including 12% who developed life threatening neurologic complications [22].
The purpose of this critical review is to summarize current mechanistic theories of neurologic complications in both adult and pediatric patients with SARS-CoV-2 infection. A deeper understanding of the mechanisms behind these manifestations can lead to targeted therapeutic interventions and improved patient outcomes.

2. Neural Tissue

There is increased urgency to investigate the cause(s) of neurologic complications in patients infected with SARS-CoV-2. Approximately one in seven hospitalized adults who are SARS-CoV-2 positive develop neurologic complications secondary to infection. Severe manifestations include toxic/metabolic encephalopathy, seizure, stroke, and hypoxic/ischemic injury [23]. Long-term neurologic sequelae in COVID-19 survivors include an increased burden of nervous system disorders, neurocognitive dysfunction, and psychiatric issues [24]. As the medical literature grows, identifiable trends may shed light on the underlying mechanisms, treatment modalities, and outcomes.

Understanding the pathophysiology of neurologic involvement in pediatric populations may aid our understanding of the neuroinflammatory changes seen in the context of SARS-CoV-2 infection. Multisystem inflammatory syndrome in children (MIS-C), a post-infection hyperinflammatory response, with associated neurologic complications portends serious outcomes in children and adolescents. Complications include diffuse CNS involvement (CNS infection, acute disseminated encephalomyelitis, severe encephalopathy, and acute fulminant cerebral edema) and vessel and peripheral nerve disorders (Guillain–Barre syndrome and variants) [25]. In a study of 1695 hospitalized pediatric patients admitted with either acute COVID-19 pneumonia or MIS-C, although the majority (88%) of children developed transient neurologic complications (such as headache and seizure) that resolved by the time of discharge, 12% of hospitalized patients developed life-threatening neurologic complications [26]. Not surprisingly, children who developed more severe neurologic manifestations had a higher neutrophil-to-lymphocyte ratios and D-Dimer level, indicating increased inflammation and coagulopathy [22]. Significant elevation of inflammatory markers including erythrocyte sedimentation rate (ESR), C-reactive protein, D-dimer, and fibrinogen are seen in patients with MIS-C [26]. The long-term neurologic and psychiatric implications of this inflammation are still largely unknown and determining the underlying mechanism of neurologic sequela in children infected with SARS-CoV-2 is imperative for identifying neuroprotective therapies.

Due to widespread reports of anosmia and ageusia in adult COVID-19 patients [27,28], it was initially hypothesized that SARS-CoV-2 may cross the blood–brain barrier. Initial studies reported the presence of the COVID-19 spike protein (S1) within olfactory nerves as well as viral mRNA samples within the cerebrospinal fluid, suggesting that the virus may be able to enter the central nervous system and induce neural dysfunction with resulting neuroinflammation [29]. However, new available information regarding SARS-CoV-2’s ability to invade the central nervous system has undermined this theory. Newer evidence suggests that it is the host’s immune response to SARS-CoV-2 infection that is responsible for the neurologic complications secondary to viral infection. Immune cells mitigate viral infectivity by initiating an inflammatory response through the release of pro-inflammatory cytokines (most notably, IL-1, IL-6, IL-8, MCP-1, and tumor necrosis factor [TNF]) [30]. Hypercytokinemia, also known as a cytokine storm, occurs during a systemic inflammatory response resulting in signaling dysregulation and increased oxidative stress that can lead to neuronal damage and subsequent neuroinflammation [31].

3. Blood Vessels

There have been a number of hypotheses seeking to establish a link between SARS-CoV-2 and stroke. The predominant theory suggests coagulopathy and inflammation related to endothelial dysfunction develop in small to medium-size vessels [32]. SARS-CoV-2 has been associated with sepsis-induced coagulopathy leading to life-threatening disseminated intravascular coagulation (DIC). Multiple studies show virally infected pa-
3. Blood Vessels

There have been a number of hypotheses seeking to establish a link between SARS-CoV-2 and stroke. The predominant theory suggests coagulopathy and inflammation related to endothelial dysfunction develop in small to medium-size vessels [32]. SARS-CoV-2 has been associated with sepsis-induced coagulopathy leading to life-threatening disseminated intravascular coagulation (DIC). Multiple studies show virally infected patients have a lower prothrombin activity, elevated D-dimer, and thrombocytopenia leading to microvascular thrombosis, endothelial dysfunction, and end-organ failure [32]. Additionally, patients with COVID-19 who tested positive for antiphospholipid (APL) antibodies and anti-β2-glycoprotein antibodies had a higher incidence of cerebral infarction [33,34]. Another theorized mechanism of the development of stroke in SARS-CoV-2 is viral interaction with the angiotensin II receptor. The virus has been shown to deplete angiotensin-converting enzyme-II (ACE-II) via receptor-mediated endocytosis, in turn inducing an increase in systemic angiotensin II [35] and possibly exacerbating systemic inflammation. This inflammation may lead to an increase in tissue factor (TF), contributing to hypercoagulation or blood–brain barrier leakage and resulting in ischemic or hemorrhagic stroke, as depicted in Figure 1 [36]. Furthermore, recombinant ACE-II therapy has been found to prevent acute stroke in the setting of a COVID-19 infection in addition to routine anticoagulation with tissue plasminogen activator (tPA), low molecular weight heparin (LMWH), and/or full-dose heparin [35].

4. Conclusions

Due to the prevalence of neurologic complications, there is an urgent need to assess the underlying mechanisms of CNS involvement in SARS-CoV-2 infection. To optimize treatment modalities, it is essential to investigate the underlying pathways of neuroinflammation. If the virus itself is responsible, utilizing an antiviral agent may help prevent severe neurologic outcomes. On the contrary, if it is due to the host’s immune response and hypercytokinemia, then optimal treatment would consist of a more targeted immunosuppressive therapy. Although the long-term sequelae of neurologic complications and neuroinflammation in patients with SARS-CoV-2 infection are still unknown, it will likely pose a significant obstacle to neurologic recovery and future studies will be required to optimize outcomes.

The hypothesis of the neuropathogenesis related with COVID-19 infection is as follows: Vascular and neuro cytokine storm, neurotropism of the virus, and activation of neuroinflammation.

Figure 1. COVID-19 in the vascular system and neural tissue: (1): vessel; (2): BBB (blood–brain barrier); (3): circumventricular organs; (4): presynaptic terminal; (5): post synaptic terminal; (6): microglia; (7): astrocyte.
flammatory cells mediate stroke and epileptiform abnormalities, resulting in cognitive deficit and seizures.

**Author Contributions:** Conceptualization of the manuscript and figure, A.E.M.; writing—original draft preparation and review and editing, K.H., T.W., E.F., H.O., E.P., J.H., Z.G. and A.E.M.; editing figure, E.P. and A.E.M. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** BioRender for the software to create the figure and Aravich for his comments.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Dafer, R.M.; Osteraa, N.D.; Biller, J. Acute Stroke Care in the Coronavirus Disease 2019 Pandemic. *J. Stroke Cerebrovasc. Dis.* 2020, 29, 104881. [CrossRef] [PubMed]

2. Morassi, M.; Bagatto, D.; Cobelli, M.; D’Agostini, S.; Gigli, G.L.; Gnà, C.; Vogrign, A. Stroke in patients with SARS-CoV-2 infection: Case series. *J. Neurol.* 2020, 267, 2185–2192. [CrossRef] [PubMed]

3. Beyrouti, R.; Adams, M.E.; Benjamin, L.; Cohen, H.; Farmer, S.F.; Goh, Y.Y.; Humphries, F.; Jäger, H.R.; Losseff, N.A.; Perry, R.J.; et al. Characteristics of ischaemic stroke associated with COVID-19. *J. Neurol. Neurosurg. Psychiatry* 2020, 91, 889–891. [CrossRef] [PubMed]

4. Hughes, C.; Nichols, T.; Pike, M.; Subbe, C.; Elghenzai, S. Cerebral Venous Sinus Thrombosis as a Presentation of COVID-19. *Eur. J. Case Rep. Intern. Med.* 2020. [CrossRef]

5. Majidi, S.; Fifi, J.T.; Ladner, T.R.; Lara-Reyna, J.; Yaeger, K.A.; Yim, B.; Dangayach, N.; Oxley, T.J.; Shimatsumi, T.; Kummer, B.R.; et al. Emergent Large Vessel Occlusion Stroke During New York City’s COVID-19 Outbreak. *Stroke* 2020, 51, 2656–2663. [CrossRef]

6. Oxley, T.J.; Mocco, J.; Majidi, S.; Kellner, C.P.; Shoibrah, H.; Singh, I.P.; De Leacy, R.A.; Shimatsumi, T.; Ladner, T.R.; Yaeger, K.A.; et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *J. Neurol. Med.* 2020, 382, e60. [CrossRef]

7. Helms, J.; Kremer, S.; Merdij, H.; Clere-Jehl, R.; Schenek, M.; Kummerlen, C.; Collange, O.; Boulay, C.; Fafi-Kremer, S.; Ohana, M.; et al. Neurologic Features in Severe SARS-CoV-2 Infection. *J. Neurol. Med.* 2020, 382, 2268–2270. [CrossRef]

8. Farhadian, S.F.; Glick, L.R.; Vogels, C.B.F.; Thomas, J.; Chiarella, J.; Casanovas-Massana, A.; Zhou, J.; Odio, C.; Vijayakumar, P.; Geng, B.; et al. Acute encephalopathy with elevated CSF inflammatory markers as the initial presentation of COVID-19. *BMC Neurol.* 2020, 20, 248. [CrossRef]

9. Poyiadji, N.; Shahin, G.; Noujaim, D.; Stone, M.; Patel, S.; Griffith, B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: Imaging Features. *Radiology* 2020, 296, E191–E200. [CrossRef]

10. Delamarre, L.; Gollion, C.; Grouette, G.; Roussel, D.; Jimena, G.; Roustan, J.; Gaussen, F.; Aldigé, E.; Gaffard, C.; Duplantier, J.; et al. COVID-19–associated acute necrotising encephalopathy successfully treated with steroids and polyclonal immunoglobulin with unusual IgG targeting the cerebral fibre network. *J. Neurol. Neurosurg. Psychiatry* 2020, 91, 1004–1006. [CrossRef]

11. Parauda, S.C.; Gao, V.; Gewirtz, A.N.; Parikh, N.S.; Berkley, A.E.; Lantos, J.; White, H.; Kishore, D.; Navi, B.B.; Segal, A.Z. Posterior reversible encephalopathy syndrome in patients with COVID-19. *J. Neurol. Sci.* 2020, 416, 117019. [CrossRef]

12. Morishige, T.; Harui, N.; Goto, J.; Harada, S.; Sugawara, H.; Takamino, J.; Ueno, M.; Sakata, H.; Kondo, K.; Myose, N.; et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Brain* 2020, 150, 2603–2612. [CrossRef]

13. Etemadifar, M.; Salari, M.; Murgai, A.A.; Hajiahmadi, S. Fulminant encephalitis as a sole manifestation of COVID-19. *Clin. Transl. Neurosci.* 2022, 6, 1.

14. Hepburn, M.; Mullaguri, N.; George, P.; Hantus, S.; Punia, V.; Bhimraj, A.; Newey, C.R. Acute Symptomatic Seizures in Critically Ill Patients with COVID-19: Is There an Association? *Neurocrit. Care* 2020, 34, 139–143. [CrossRef]

15. Sohal, S.; Mansur, M. COVID-19 Presenting with Seizures. *IDCases* 2020, 20, e00782. [CrossRef]

16. AlKetbi, R.; AlNuaimi, D.; AlMulla, M.; AlTalai, N.; Samir, M.; Kumar, N.; AlBastaki, U. Acute myelitis as a neurological complication of Covid-19: A case report and MRI findings. *Radiol. Case Rep.* 2020, 15, 1591–1595. [CrossRef]

17. Valiuddin, H.; Skwirski, B.; Paz-Arabo, P. Acute transverse myelitis associated with SARS-CoV-2: A Case-Report. *Brain Behav. Immun. Health* 2020, 5, 100091. [CrossRef]

18. Chakraborty, U.; Chandra, A.; Ray, A.K.; Biswas, P. COVID-19–associated acute transverse myelitis: A rare entity. *BMJ Case Rep.* 2020, 13, e238668. [CrossRef]

19. 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.* 2020, 268, 1133–1170. [CrossRef]
20. Uncini, A.; Vallat, J.-M.; Jacobs, B.C. Guillain-Barré syndrome in SARS-CoV-2 infection: An instant systematic review of the first six months of pandemic. *J. Neurol. Neurosurg. Psychiatry* 2020, 91, 1105–1110. [CrossRef]

21. Varatharaj, A.; Thomas, N.; Ellul, M.A.; Davies, N.W.S.; A Pollak, T.; Tenorio, E.L.; Sultan, M.; Easton, A.; Breen, G.; Zandi, M.; et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: A UK-wide surveillance study. *Lancet Psychiatry* 2021, 7, 875–882. [CrossRef]

22. LaRovere, K.L.; Riggs, B.J.; Foussaint, T.Y.; Young, C.C.; Newhams, M.M.; Maamari, M.; Walker, T.C.; Singh, A.R.; Dapul, H.; Hobbs, C.V.; et al. Neurologic Involvement in Children and Adolescents Hospitalized in the United States for COVID-19 or Multisystem Inflammatory Syndrome. *JAMA Neurol.* 2021, 78, 536. [CrossRef]

23. Frontera, J.A.; Sabadia, S.; Lalchan, R.; Fang, T.; Flusty, B.; Millar-Vernetti, P.; Snyder, T.; Berger, S.; Yang, D.; Granger, A.; et al. A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City. *Neurology* 2020, 96, e575–e586. [CrossRef]

24. Al-Aly, Z.; Xie, Y.; Bowe, B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* 2021, 594, 259–264. [CrossRef]

25. Paterson, R.W.; Brown, R.L.; Benjamin, L.; Nortley, R.; Wiethoff, S.; Bharucha, T.; Jayaseelan, D.L.; Kumar, G.; Raftopoulos, R.E.; Zambreanu, L.; et al. The emerging spectrum of COVID-19 neurology: Clinical, radiological and laboratory findings. *Brain* 2020, 143, 3104–3120. [CrossRef]

26. Feldstein, L.R.; Rose, E.B.; Horwitz, S.M.; Collins, J.P.; Newhams, M.M.; Son, M.B.F.; Newburger, J.W.; Kleinman, L.C.; Heidemann, S.M.; Martin, A.A.; et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *N. Engl. J. Med.* 2020, 383, 334–346. [CrossRef]

27. Lechien, J.R.; Chiesa-Estomba, C.M.; De Siati, D.R.; Horoi, M.; Le Bon, S.D.; Rodriguez, A.; Dequanter, D.; Blebic, S.; El Afia, F.; Distinguin, L.; et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): A multicenter European study. *Eur. Arch. Oto-Rhino-Laryngol.* 2020, 277, 2251–2261. [CrossRef]

28. Benezit, F.; Le Turnier, P.; Declerck, C.; Paillé, C.; Revest, M.; Dubée, V.; Tattevin, P.; for the RAN COVID Study Group. Utility of hyposmia and hypogeusia for the diagnosis of COVID-19. *Lancet Infect. Dis.* 2020, 20, 1014–1015. [CrossRef]

29. Qi, X.; Keith, K.A.; Huang, J.H. COVID-19 and stroke: A review. *Hemorrhagic Stroke* 2020. [CrossRef] [PubMed]

30. Zhang, Y.; Xiao, M.; Zhang, S.; Xia, P.; Cao, W.; Jiang, W.; Chen, H.; Ding, X.; Zhao, H.; et al. Antiphospholipid Antibodies in Critically Ill Patients With COVID-19. *Arthritis Rheumatol.* 2020, 72, 1998–2004. [CrossRef] [PubMed]

31. Hess, D.C.; Eldahshan, W.; Rutkowski, E. COVID-19-Related Stroke. *Transl. Stroke Res.* 2020, 11, 322–325. [CrossRef]

32. Wang, Z.; Yang, Y.; Jiang, X.; Gao, B.; Liu, M.; Li, W.; Chen, Z.; Wang, Z. COVID-19 Associated Ischemic Stroke and Hemorrhagic Stroke: Incidence, Potential Pathological Mechanism, and Management. *Front. Neurol.* 2020, 11, 571996. [CrossRef]