Putative autoimmune mechanisms for Acute Disseminated Encephalomyelitis (ADEM) and Guillain-Barré Syndrome (GBS) associated with SARS-CoV-2 infection

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Abstract
The novel coronavirus severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, responsible for the ongoing COVID-19 pandemic, is associated with a broad manifestation of neurological disease, including Acute Disseminated Encephalomyelitis (ADEM) and Guillain-Barré Syndrome (GBS), amongst other forms of autoimmune encephalitis, stroke, encephalopathy, delirium, and cranial neuropathies. These phenomena are not limited to human coronaviruses but are also seen in a minority of patients in response to other viral infection. There is good evidence that an autoimmune mechanism hypothesis is likely. The final pathology is probably the culmination of mixed mechanisms such as vascular and immune dysregulation as well as direct viral invasion of neurons – though there is little if any evidence of viral invasion in the literature to date. The aim of this review is to elucidate the emerging evidence about this subset of COVID-19-associated neurological disease. This unique opportunity to study the interactions between virus and host immune and central nervous system (CNS) to gain novel insights applicable to other probable autoimmune neurological disease. I have conducted a literature search as well as drawn on my own observations from the COVID-19 and encephalitis multidisciplinary meetings at Queen Square National Hospital for Neurology and Neurosurgery, London, UK.

Though rare, involvement of the CNS during or after viral infection results in serious disease. This is the case in the minority of patients with severe COVID-19. COVID-19 is the result of infection by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first identified in Wuhan, China in November 2019, causing flu-like illness in most infected patients and severe pneumonia and/or death in a minority. The emerging evidence for neurological disease during or following COVID-19 is an echo of what took place during the SARS and MERS pandemics – a spectrum of both inflammatory and ischaemic disease processes. Here I focus on ADEM-like disease (as a subset of Autoimmune Encephalitis (AE)) and GBS associated with COVID-19. ADEM is characterised clinically by the acute onset of polyfocal neurological symptoms such as pyramidal signs, ataxia, hemiparesis, optic neuritis and other cranial nerve involvement, and seizures, presenting with highest frequency in childhood [1]. GBS is a peripheral neuropathy, which presents as progressive bilateral weakness of the arms and/or legs in the absence of CNS involvement. Progression is rapid, with the majority of patients with GBS reaching their maximum disability in two weeks resulting in paresis of the limb, cranial and respiratory musculature [2]. I will discuss existing and emerging evidence supporting each of the following theories: a) autoantibody production via i) molecular mimicry or ii) other means; b) systemic immune dysregulation; and c) neuronal damage via direct viral invasion. The development of ADEM has already been linked to precedent infectious, particularly viral, disease [1] and GBS to a variety of viruses and to a number of other pandemics, such as Zika Virus, MERS-CoV and SARS-CoV [3]. It is known that autoantibody production in GBS drives axonal degeneration in pathogenesis. It is believed that both these diseases develop as the result of a similar autoimmune mechanism.

COVID-19-associated neurological disease

The spectrum of neurological disease associated with COVID-19 is broad [4,5,6,7]. A recent study of patients at Queen Square outlined 4 major categories of neurological disease manifestation [8] – encephalopathies with delirium, inflammatory CNS syndromes (including ADEM) and peripheral neurological disorders (including GBS), though vasculopathies, such as ischaemic and haemorrhagic stroke seem to dominate, which is understandable in the context of COVID-19 assoicated lung and vascular injury. They reported a 'striking' incidence of ADEM amongst their patients, which did not correlate with lung disease severity [9], suggesting that pathogenesis mechanisms of inflammatory lung and brain tissue damage differ. In support of this, some cases

of neurological disease have preceded lung disease [3]. Notwithstanding, it is known that hypoxia, the effects of systemic infection, critical illness and hypertension have been associated with encephalopathy. This puts the spectrum of COVID-19-associated neurological disease into context when considering that most patients with severe neurological symptoms have been admitted to ITU and are in significantly poor health.

Autoimmune disease via autoantibody production

Evidence supporting an autoimmune mechanism for neurological disease coincidental with SARS-CoV-2 infection comes from individual case studies with the following clinical features: a) positive autoantibody screen; and b) clinical features which resemble neurological disease of known autoimmune origin. In addition, the mere fact that COVID-19 has been associated with outbreaks of GBS [10] warrants suspicion of an autoimmune mechanism. However, there is still some controversy over whether COVID-19 is truly associated with these cases [11].

Several case studies of patients with probable AE and/or GBS have reported the detection of autoantibodies. Gutiérrez-Ortiz et al. describe the case of a patient positive for anti-GD1b-IgG and Miller-Fisher syndrome after acute SARS-CoV-2 infection. Yet in the same case report, they identified a patient with probable polyneuritis cranialis with a negative autoantibody screen [12]. In the same vein, several groups have reported anti-GM and anti-GD1b IgG positive post-COVID patients with GBS [13,14]. In most of these cases of GBS, titre of both SARS-CoV-2 and identified autoantibody was lower or not present in CSF and higher in plasma, suggestive of a mechanism involving autoantibody production outside of the CNS and excluding one which involves SARS-CoV-2 interacting with the privileged immune system of the CNS. In terms of ADEM, Grimaldi et al. describe the case of a patient who was positive for autoantibodies to the nuclei of Purkinje cells, striatal and hippocampal neurons in CSF and plasma, though the identity of the specific antigen involved was unknown and the synthesis of these autoantibodies has not been reported in any other case of autoimmune encephalitis [15]. Another case showed positive CSF examinations for NMDAR and GFAP antibodies [16].

It is important to highlight that the majority of cases of ADEM and GBS report negative broad immunological screens in CSF and serum (for autoantibodies against Caspr 2, LGi1, NMDAR, anti-Hu, anti-GAD, anti-aquaporin 4 and anti-DPPX) [8,17,18,19,20]. The fact that most GBS and AE cases associated with SARS-CoV-2 are seronegative does not rule out an autoimmune mechanism. The literature on probable seronegative neuroautoimmune disorders is established and may reflect the situation for SARS-CoV-2-associated autoimmune disease [21]. It is thought that pathogenesis in seronegative patients with clear autoimmune disease either results from the production of an undetected or uncharacterised autoantibody, or that pathogenesis is wholly different and not dependent on autoantibody production. Firstly, there are subtypes of GBS for which no specific autoantibody has yet been discovered, in addition to well-known autoantibodies for GM1, GD1a, GA1Nac-GD1a, GD1b and GQ1b ganglioside antibodies, which could explain why recent case studies of GBS in the context of COVID-19 show either no CSF abnormalities or a mixture amongst patients, as described previously [3,8,15,22,23,24]. Antibody detection in cases of GBS in association with Zika virus have been equally poor as for AE in COVID-19 [25]. Interestingly, Zhao et al. describe the first reported case of GBS in coincidence with COVID-19 before the manifestation of typical symptoms and RT-PCR detection of SARS-CoV-2 on nasopharyngeal swab [24]. This suggests a para-infectious rather than post-infectious disease process, which is in agreement with other studies which report the temporal coincidence of neurological symptoms with fever, myalgia and other typical 'early' COVID-19 symptoms [8,26].

In support of the latter possibility that COVID-19-associated GBS and AE result from different disease mechanisms, infection-triggered autoantibody production does not always result in clinical disease: for example, in a follow up study of HSV encephalitis patients, whilst 27% went on to develop anti-NMDAR autoimmune encephalitis, 3 patients synthesised anti-NMDAR autoantibodies asymptomatically [27]. Further, Keddie et al. found no significant similarities between the SARS-CoV-2 genome and human genome, suggesting that molecular mimicry – a typical mechanism of virus-mediated autoantibody production, particularly in GBS – might not be taking place [11]. Immune hyperactivity or 'cytokine storm syndrome' (CSS) are involved in the manifestation of COVID-19-associated neurological disease in general [28]. Numerous cases of GBS and ADEM show the typical screen of elevated cytokines characteristic of CSS. Therefore, it is likely that a combination of mechanisms starting with systemic SARS-CoV-2 infection take place to result in autoimmune disease. These mechanisms manifest heterogeneously amongst patients depending on individual factors, such as genetics. For example, it has been shown that a number of HLA phenotypes predispose to COVID-19-associated GBS [29].

Autoimmune-like clinical features

Brain imaging of COVID-19 brain disease frequently shows pathological lesions that are also characteristic of ADEM and AHLE [30]. Paterson et al. describe the typical radiological presentations of ADEM-like COVID patients: multifocal white matter hyperintense lesions on FLAIR, in association with haemorrhagic lesions in some - in the Queen Square study, 8 out of 43 patients had vascular or microvascular presentations but the high incidence of haemorrhagic changes on imaging across all categories of neurological disease were startling [8,31]. Furthermore, other biopsy studies show some signs of ADEM-like histological appearance: small white matter lesions with clusters of macrophages with variability in axonal injury and perivenular association [32]. But histopathological findings in one patient with white matter microbleeds showed lymphohistiocytic inflammation, suggestive of cytokine storm-induced lymphocyte recruitment [33] - it is not entirely clear whether white matter changes seen in imaging and histopathology studies are secondary to vascular insults or the result of immune-mediated demyelination, and whether this occurs downstream of autoimmune disease or is a primary dysregulation of the immune disease in its own right [34]. It is widely known that inborn toll-like receptor 3 (TLR3) mutations cause Herpes Simplex Encephalitis (HSE) as a result of inappropriate immune response to Herpes Simplex virus 1 (HSV-1) [35]. It is possible that encephalitic disease can originate at the level of the immune system and that, perhaps, COVID-related disease shares some aspects of this. Plus, it is well-known that levels of pro-inflammatory markers, such as IL-6 in particular, increase with disease severity [36] and that several genetic polymorphisms responsible for physiological immune function have been associated with COVID-19 susceptibility [37]. These patients also have higher numbers of FCN1+ macrophages in the airways as well as CD14+CD16+ monocytes in peripheral blood smears, which are responsible for the supposed CSS which causes extreme disease and even fatality in COVID-19 [28]. Pilotto et al. report a case of COVID-19 associated encephalitis where the patient was CSF-negative for SARS-CoV-2 but with a high level of IL-8 and TNFα in the CSF [38]. It is these high levels of circulating cytokines which result in systemic disease and may be equally important in the context of neurological disease manifestation. It is possible that final observed pathology is a combination of disease processes occurring simultaneously. This would explain the broad spectrum of COVID-19 associated neurological disease.

This combination of pathogenic mechanisms could arise through a 'multiple hit' manner, where consecutive immunological challenge, resulting in autoantibody production or otherwise, results in disease. In support of this, Panariello et al. report the case of a psychotic patient with a history of substance use disorder – it is known that exogenous substances such as ketamine can induce anti-NMDAR encephalitis [39] – with clinical signs of COVID-19 and no response to antipsychotics. Upon worsening encephalitic symptoms, CSF analysis revealed anti-NMDAR antibodies and a diagnosis of anti-NMDAR autoimmune encephalitis was made [16]. It is possible that COVID-19 and the spectrum of its systemic and immune effects, such as CSS-type effects, provided the final step to bring this particular patient to disease threshold. This would also explain why a subset of COVID-19

patients present with GBS and ADEM after a delay [40], as is the case with a range of neuroautoimmune diseases which result from secondary autoantibody production upon immunogenic challenge of multiple epitopes.

Neuronal damage via direct viral entry

On the other hand, it is argued that rather than causing classical autoimmune disease, SARS-CoV-2 causes neurological damage by directly invading the CNS. SARS-CoV-2 is a cytopathic virus, meaning that it gains entry to host cells – via ACE2 and TMPRSS2 surface receptors - and induces cell death and injury. A contradiction to the autoimmune hypothesis for ADEM is the presence of SARS-CoV-2 in the CSF and biopsy samples in a number of case studies [41], though rarely in cases of GBS [20]. Moreover, it has been posited that SARS-CoV-2, like SARS-CoV, has neuroinvasive potential and spreads to the CNS via the olfactory bulb and nerve through the cribriform plate and olfactory epithelium, accounting for the widespread reporting of symptoms of anosmia and hyposmia amongst COVID-19 patients [42]. The expression of ACE2 on olfactory epithelia and, further, reported in areas of the brain by several studies, suggest that the virus can directly infect a wide range of neurons.

SARS-CoV has been reliably extracted from autopsy specimens of patients who died as a result of SARS, in particular in neurons of the cortex and hypothalamus, and ACE2 is strongly expressed in the ventrolateral medulla and the nucleus of the tractus solitarus [41]. Similarly, histopathology studies of COVID-19 patients found neuronal cell loss and axonal degeneration in the dorsal motor nuclei of CN X, CN V, nucleus of the tractus solitaris, the dorsal raphe nuclei and fasciculus longitudinalis, though it is difficult to say whether these widespread neuronal insults were the result of direct viral infection or an immune response.

However, evidence of viral CNS entry by analysis of CSF across case studies has proven inconclusive: none of the patients in the Queen Square study had tested positive for SARS-CoV-2 RT-PCR CSF and data is mixed amongst other studies [4,9,36,43,44]. Moreover, treatment for COVID-19 with antivirals has been discontinued following advice from the WHO, with reports conflicting over their efficacy. But, a single case study of probable acute encephalitis in association with SARS-CoV-2 and positive CSF result has been reported, which should lead us not to undermine the neuro-invasive potential of this virus [9].

Conclusion

Whilst I argue for an autoimmune-mediated mechanism, or at least an autoimmune trigger to detectable disease, there is a great amount of conflicting evidence in support of several different hypotheses, namely viral infiltration or a broader systemic 'cytokine storm'. Rather than being competitors, it seems likely that these mechanisms must be non-exclusive and must add up uniquely within each patient, accounting for the variability in neurological presentation in association with COVID-19. Such a collaboration of disease processes would explain why outcome also differs so much between individuals of different ethnic groups, ages, and past medical history. The implication for a multifactorial pathogenesis is that there may be no universal effective treatment. It is therefore imperative that neurological cases associated with COVID-19 are examined with care to understand if one mechanism dominates. This could, for example, either guide treatment towards steroidal agents for a CSS-dominant pathogenesis or intravenous immunoglobulin therapies to treat autoantibody-dominant mechanisms. Encephalitis Lethargica (EL) so-called postencephalitic parkinsonism which take decades to manifest itself and is estimated to have affected 1 million people between 1915 and 1930 [45]. The highly elusive relationship between the influenza pandemic of 1916-1918 and the EL pandemic should prompt us to question the role of viral infection in long-term neurological disease. Whilst it is currently hard to both dissect the true relationship between COVID-19 and neuroautoimmune diseases, and to predict what is to come following COVID-19, our understanding of its neurological effects will be crucial in preventing a similar outcome.

References

1. Pohl D, et al. Acute disseminated encephalomyelitis: Updates on an inflammatory CNS syndrome. Neurology. 2016;87(9 Suppl 2):S38-45. https://doi.org/10.1212/WNL.0000000000002825
2. Leonhard SE, et al. Diagnosis and management of Guillain-Barré syndrome in ten steps. Nature Reviews Neurology. 2019;15(11):671-683. https://doi.org/10.1038/s41582-019-0250-9
3. Dalakas MC. Guillain-Barré syndrome: The first documented COVID-19-triggered autoimmune neurologic disease. More to come with myositis in the offing. 2020;7(5):e781. https://doi.org/10.1212/NXI.0000000000000781
4. Ahmed MU, et al. Neurological Manifestations of COVID-19 (SARS-CoV-2): A Review. Frontiers in Neurology. 2020;11(518). https://doi.org/10.3389/fneur.2020.00518
5. Mao L, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurology. 2020;77(6):683-690. https://doi.org/10.1001/jamaneurol.2020.1127
6. Rogers JP, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. The Lancet Psychiatry. 2020;7(7):611-627. https://doi.org/10.1016/S2215-0366(20)30203-0
7. Ellul MA, et al. Neurological associations of COVID-19. The Lancet Neurology. 2020; 19(9):767-783. https://doi.org/10.1016/S1474-4422(20)30221-0
8. Paterson RW, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain. 2020.
9. Moriguchi T, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. International Journal of Infectious Diseases. 2020;94:55-58. https://doi.org/10.1016/j.ijid.2020.03.062
10. Toscano G, et al. Guillain-Barré Syndrome Associated with SARS-CoV-2. New England Journal of Medicine. 2020;382(26):2574-2576. https://doi.org/10.1056/NEJMc2009191
11. Keddie S, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. Brain. 2021;144(2):682-693. https://doi.org/10.1093/brain/awaa433
12. Gutiérrez-Ortiz C, et al. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. Neurology. 2020;95(5):e601-e605. https://doi.org/10.1212/WNL.0000000000009619
13. Diez-Porras L, et al. Guillain-Barré-Strohl syndrome and COVID-19: Case report and literature review. Neuromuscul Disord. 2020;30(10):859-861. https://doi.org/10.1016/j.nmd.2020.08.354
14. Civardi C, et al. Antiganglioside antibodies in Guillain-Barré syndrome associated with SARS-CoV-2 infection. J Neurol Neurosurg Psychiatry. 2020;91(12):1361-1362. https://doi.org/10.1136/jnnp-2020-324279
15. Grimaldi S, et al. Autoimmune encephalitis concomitant with SARS-CoV-2 infection: insight from 18F-FDG PET imaging and neuronal autoantibodies. Journal of Nuclear Medicine. 2020. https://doi.org/10.2967/jnumed.120.249292
16. Panariello A, et al. Anti-NMDA receptor encephalitis in a psychiatric COVID-19 patient: A case report. Brain Behav Immun. 2020;87:179-181. https://doi.org/10.1016/j.bbi.2020.05.054
17. Zambreanu L, et al. A case of limbic encephalitis associated with asymptomatic COVID-19 infection. Journal of Neurology, Neurosurgery & Psychiatry. 2020:p. jnnp-2020-323839. https://doi.org/10.1136/jnnp-2020-323839
18. Pilotto A, et al. Steroid-Responsive Encephalitis in Coronavirus Disease 2019. Annals of Neurology. 2020;88(2):423-427. https://doi.org/10.1002/ana.25783
19. Delamarre L, et al. COVID-19-associated acute necrotising encephalopathy successfully treated with steroids and polyvalent immunoglobulin with unusual IgG targeting the cerebral fibre network. Journal of Neurology, Neurosurgery & Psychiatry. 2020;91(9):1004-1006. https://doi.org/10.1136/jnnp-2020-323678
20. Freire M, et al. Guillain Barré syndrome associated with COVID-19- lessons learned about its pathogenesis during the first year of the pandemic, a systematic review. Autoimmun Rev. 2021;20(8):102875. https://doi.org/10.1016/j.autrev.2021.102875
21. Alessandri C, et al. Seronegative Autoimmune Diseases. Annals of the New York Academy of Sciences. 2009;1173(1):52-59. https://doi.org/10.1111/j.1749-6632.2009.04806.x
22. Khoo A. et al. Postinfectious brainstem encephalitis associated with SARS-CoV-2. Journal of Neurology, Neurosurgery & Psychiatry. 2020;91(9):1013-1014. https://doi.org/10.1136/jnnp-2020-323816
23. Zanin L, et al. SARS-CoV-2 can induce brain and spine demyelinating lesions. Acta neurochirurgica. 2020;162(7):1491-1494. https://doi.org/10.1007/s00701-020-04374-x
24. Zhao H, et al. Guillain-Barre; syndrome associated with SARS-CoV-2 infection: causality or coincidence? The Lancet Neurology. 2020;19(5):383-384. https://doi.org/10.1016/S1474-4422(20)30109-5
25. Cao-Lormeau VM, et al. Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. Lancet. 2016;387(10027):1531-1539. https://doi.org/10.1016/S0140-6736(16)00562-6
26. McAbee GN, et al. Encephalitis Associated with COVID-19 Infection in an 11-Year-Old Child. Pediatric Neurology. 2020;109:94. https://doi.org/10.1016/j.pediatrneurol.2020.04.013

27. Armangue T, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. Lancet Neurol. 2018;17(9):760-772. ttps://doi.org/10.1016/S1474-4422(18)30244-8
28. Tay MZ, et al. The trinity of COVID-19: immunity, inflammation and intervention. Nature Reviews Immunology. 2020;20(6):363-374. https://doi.org/10.1038/s41577-020-0311-8
29. Gigli GL, et al. HLA and immunological features of SARS-CoV-2-induced Guillain-Barré syndrome. Neurol Sci. 2020;41(12):3391-3394. https://doi.org/10.1007/s10072-020-04787-7
30. V Montalvan JL, Bueso T, De Toledo J, Rivas K. Neurological Manifestations of COVID-19 and other coronavirus infections: a systematic review. Clinical Neurology and Neurosurgery. 2020;(194). https://doi.org/10.1016/j.clineuro.2020.105921
31. Kremer PS, et al. Brain MRI Findings in Severe COVID-19: A Retrospective Observational Study. Radiology. 0(0): p. 202222.
32. von Weyhern CH, et al. Early evidence of pronounced brain involvement in fatal COVID-19 outcomes. The Lancet, 2020. 395(10241): p. e109. https://doi.org/10.1016/S0140-6736(20)31282-4
33. Jaunmuktane Z, et al. Microvascular injury and hypoxic damage: emerging neuropathological signatures in COVID-19. Acta Neuropathologica., 2020;140(3):397-400. https://doi.org/10.1007/s00401-020-02190-2
34. Reichard RR, et al. Neuropathology of COVID-19: a spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. Acta Neuropathologica. 2020; 140(1):1-6. https://doi.org/10.1007/s00401-020-02166-2
35. Zhang SY, Casanova JL. Inborn errors underlying herpes simplex encephalitis: From TLR3 to IRF3. J Exp Med. 2015;212(9):1342-3. https://doi.org/10.1084/jem.2129insight4
36. Mariotto S, et al. Nervous system: subclinical target of SARS-CoV-2 infection. Journal of Neurology, Neurosurgery & Psychiatry. 2020;91(9):1010-1012. https://doi.org/10.1136/jnnp-2020-323881
37. Ellinghaus D, et al. Genomewide Association Study of Severe COVID-19 with Respiratory Failure. New England Journal of Medicine. 2020.
38. Pilotto A, et al. Steroid-Responsive Encephalitis in Coronavirus Disease 2019. Ann Neurol. 2020;88(2):423-427. https://doi.org/10.1002/ana.25783
39. Dalmau J, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008;7(12):1091-8. https://doi.org/10.1016/S1474-4422(08)70224-2
40. Ramos-Casals M, Brito-Zerón P, Mariette X. Systemic and organ-specific immune-related manifestations of COVID-19. Nature Reviews Rheumatology. 2021;17(6):315-332. https://doi.org/10.1038/s41584-021-00608-z
41. Zubair AS, et al. Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019: A Review. JAMA Neurology. 2020;77(8):1018-1027. https://doi.org/10.1001/jamaneurol.2020.2065
42. Cooper KW, et al. COVID-19 and the Chemical Senses: Supporting Players Take Center Stage. Neuron. 2020;107(2):219-233. https://doi.org/10.1016/j.neuron.2020.06.032
43. Natoli S, et al. Does SARS-Cov-2 invade the brain? Translational lessons from animal models. European Journal of Neurology.
44. Pilotto A, et al. The clinical spectrum of encephalitis in COVID-19 disease: the ENCOVID multicentre study. medRxiv. 2020:2020.06.19.20133991. https://doi.org/10.1101/2020.06.19.20133991
45. Hoffman LA, Vilensky JA. Encephalitis lethargica: 100 years after the epidemic. Brain. 2017;140(8):2246-2251. https://doi.org/10.1093/brain/awx177