Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: January 31, 2023

Citation: Miguel Valdés J, Vivanco F, et al., 2022. Covid-19 Related Encephalopathy, Medical Research Archives, [online] 11(1). https://doi.org/10.18103/mra.v11i1.3462

DOI
https://doi.org/10.18103/mra.v11i1.3462

ISSN: 2375-1924

CASE REPORT

Covid-19 Related Encephalopathy

José Miguel Valdés[1], Fernando Vivanco[2], Marianella Hernández[1], Lorna Galleguillos*[,1]

1. Department of Neurology and Psychiatry, Faculty of Medicine, Clínica Alemana-Universidad del Desarrollo, Santiago, Chile.
2. Faculty of Medicine, Clínica Alemana-Universidad del Desarrollo, Santiago, Chile.

* lgalleguillos@alemana.cl

ABSTRACT

SARS-CoV-2 infection can present with neurological symptoms due to direct or indirect invasion of the central nervous system. There are many hypotheses of why this happens, focusing on systemic inflammation, cytokines and cells, but none of them are completely understood. We present a case of a 66-year-old female that presented with a severe encephalopathy during her COVID-19 infection. We discuss physiopathology, risk factors, work up, possible treatments according to the physiopathological damage and prognosis according to the treatment response.

Introduction

SARS-CoV-2 related infection has several neurological complications, including anosmia, ageusia, headache, acute disseminated encephalomyelopathy, and Guillain-Barre syndrome,[1,2] however, the most common neurological complication of SARS-CoV-2 is encephalopathy, which has been reported in 2.3% to 28% of cases. [2–4] COVID-19-related encephalopathy has a wide spectrum of manifestations, but the principal symptoms are altered mental status, delirium, seizures, and neuropsychiatric symptoms [1,5–7]. There is no consensus when these manifestations present with different reports during the active infection or after it. The encephalopathy diagnosis usually may comply with four criteria to attribute it to the COVDI-19 infection: 1) SARS-CoV-2 diagnosis, 2) a plausible temporal relationship, 3) exclusion of alternative etiologies unrelated to SARS-CoV-2, and 4) clinical characteristics compatible with brain dysfunction secondary to systemic SARS-CoV-2. [2]

The progression of COVID-19 to an endemic state [8] reinforces the need for a better understanding of its complications and treatments, especially regarding the serious and severe neurological complications such as encephalitis or meningoencephalitis with a myriad of manifestations with a common denominator been the qualitative or quantitative involvement of the consciousness. Nevertheless, the prognosis cannot be assured today even though we are aware of the central nervous system involvement is frequent and that we need to treat as soon as possible. There is no general agreement when these manifestations can happen or if we should be screening for them in every patient independently of the COVID-19 status (active or inactive).

We present a case of COVID-19 related encephalopathy that allows us to discuss the possible pathophysiology, the different neurological manifestations, the necessary work up for the diagnosis and the benefit of different immunomodulatory and immunosuppressant therapies to treat the condition with it caveats.

Case report

66-year-old woman with a medical history of hypertension and hypothyroidism, presents with severe respiratory failure and a thorax CT compatible with COVID-19 infection, requiring intubation and being admitted to the ICU. Torpid course with slow respiratory improvement requiring tracheostomy and intubation. One month after admission, she achieves wakefulness and response to simple commands but starts with episodes of myoclonic proximal bilateral movements on the four extremities requiring sedation. The physical examination showed decreased global muscular tone with symmetrical mobilization of the 4 extremities in the context of critical patient. Because of suspected central nervous system (CNS) involvement, imaging, electrophysiological and cerebrospinal fluid studies were requested. Brain MRI ruled out tumor, ischemia, or hemorrhage; electroencephalogram (EEG) did not show epileptiform activity; cerebrospinal fluid (CSF) with normal levels of proteins and glucose with low cell count, normal CSF - IgG levels, and a negative viral meningitis panel.

After ruling out the other diagnoses, it was decided to treat it as immune-mediated chorea and encephalopathy (there was still involvement of the cognitive functions) post COVID-19. Initially, it was given benzodiazepines, levetiracetam and tetrabenazine, with poor response. It was decided to start immunoglobulin (IVIG) in a dose of 0.4gr/kilo for 5 days with regular response. New brain MRI and CSF study showed no difference with the previous ones, so the hypothesis of immune-mediated syndrome post COVID-19 was still the diagnosis with suboptimal response to first line treatment with immunoglobulin. Subsequently, it was decided to start new immunotherapy with methylprednisolone 1g daily for five days, followed by 5 days of plasmapheresis, which were well tolerated. Slowly the patient started to recover after these two treatments, decreasing the need of sedation to control the abnormal movements due to the encephalitis and full awareness again. The patient was discharged after one month due to the need of rehabilitation, but no rebound of the encephalitis has been reported in this patient till today.

Discussion

SARS-CoV-2 respiratory infection releases pro-inflammatory cytokines (IL-1b, IL-6, and TNF), which can bind to brain microvascular endothelial cells (BMECs) receptors and cause loss of tight junctions. SARS-CoV-2 binds to BMECs, and angiotensin converting enzyme 2 receptors and migrate into the brain. S1 protein binding on BMECs, and IL-1R1-induced signaling can enhance barrier breakdown and adhesion upregulation. Barrier rupture releases substances like ATP, which link to microglia receptors and activate them, resulting in enhanced phagocytosis and antigen presentation. Increased transcellular permeability promotes inflammatory myeloid cell entry, causing neuronal damage. [1,9] In the CNS, anti–SARS-CoV-2 antibodies that entered due to the blood brain

barrier (BBB) dysfunction or that are produced in the CNS compartment as a response to viral particles in the CNS, can directly induce or perpetuate neurologic damage by mobilizing complement or guiding SARS-CoV-2–infected macrophages [10,11]

Hypoxemia and hypotension produce brain tissue hypoperfusion, leading to neuronal damage secondary to glutamate toxicity, oligodendrocyte damage, blood brain barrier disruption and micro bleeding. Also, evidence of hypoxic-ischemic damage has been reported. [2]

Electrolyte disturbances, especially hyponatremia, are common findings, which may be due to several mechanisms, including IL-6 mediated vasopressin release, syndrome of inadequate anti diuretic hormone (SIADH), salt wasting syndrome, and metabolic complications (hepatic and renal failure). [2,9]

Also, it is important to mention that sepsis, multisystem organ dysfunction and cytokine storm can lead to inflammation (special role of IL-6 and increasing the permeability of the BBB, allowing invasion of immune cells in the CNS), endothelial dysfunction, micro hemorrhages and hypercoagulable states, which are known to produce encephalopathic states. [2,9]

If we only analyze the vast involvement of the CNS with SARS-Cov-2 infections and the different physiopathological ways, it is not strange to have a myriad of symptoms and presentations of this meningoencephalitis state, which can range from headache (13%), altered mental status (3,5%), confusion/disorientation (37%), focal motor deficits (22.22%), aphasia (9.25%) or visual hallucinations (3.7%) and nucal rigidity (11.11%), [12] some of which were present in our patient.

Now the problem seems to determine which of the above mentioned is the predominant pathological way that will attack the CNS and thus determine the timing of the neurological manifestations. Today there are risks factor of poor prognosis with COVID-19 infection[13], but none of these link to "when" the patient will develop the CNS involvement. The main risk factors described for developing COVID-19 encephalopathy are advanced age (>65 years), male sex and a history of comorbidities such as cancer, cerebrovascular disease, other neurological disorders, heart failure, diabetes mellitus, obesity, hypertension, chronic kidney disease and liver failure.[13] For example, a study focused on the evaluation of older adults with COVID-19 seen in the emergency department (so only one risk factor), it was shown that up to 28% had COVID-19 encephalopathy, with up to 37% being the only predominant symptom, without the other typical alterations such as fever or dyspnea which are more characteristic of the COVID-19 infection.[14.]

Among the subgroup of patients hospitalized in intensive care units, encephalopathy is commonly present between those admitted for acute respiratory distress syndrome (ARDS), such as the patient presented in this case. It has been shown that up to 84% of patients in this subgroup of patients develop encephalopathy[15], this is why it is an important cause to consider since it has a profound impact on the study, prognosis and necessary treatment of the patient.

Regarding work-up, the initial study should cover the broad spectrum of differential diagnosis with various studies. Brain MRI is the best option for structural imaging of the central nervous system complications of SARS-CoV-2. Multiple reports have described that the main alterations caused by COVID-19 are cerebrovascular, with ischemic stroke being the most common, followed by hemorrhagic stroke[15]. In the specific case of COVID-related encephalopathy, brain alterations on MRI are nonspecific, showing various changes such as white matter hyperintensity in the FLAIR signal or leptomeningeal contrast enhancement.[16] In the acute setting, a brain CT scan may be the initial approach to first rule out ischemia or hemorrhage. MRI angiography should be considered for searching vasculitis.[2] Electroencephalogram (EEG) of at least 2 to 4 hours of monitoring is recommended in patients who present with fluctuant mental status, twitching, or clinical seizures. [2] In the patient with COVID-19 encephalopathy the predominant pattern is a generalized symmetrical slowing[18]. A lumbar puncture should be performed as part of a comprehensive initial study because, as is typical in CFS, the cell count can be normal or with pleocytosis[12] with an increase in proteins in 40% of patients (>60 mg/dL). PCR of SARS-CoV-2 on CSF is only positive in 6% of patients with symptoms related to the CNS.[19] The measurement of intrathecal synthesis of IgG and more specifically SARS-CoV-2 IgG demonstrates the immune mediated process in the CNS with the presence of BBB dysfunction [10] Other studies, like autoantibody tests looking for anti NMDAR antibody is useful, especially in patients with severe, prolonged or refractory encephalopathy, even though the association exits, the risk is not high.[20]

The management of COVID-19 encephalopathy is similar to that of other critically ill patients with altered mental status. In those patients, the presence of secondary brain damage is a top priority. Some case series have reported positive outcomes when using glucocorticoids or

other immunomodulatory therapies, as in the case presented [21] due to the systemic inflammatory storm, intrathecal cellular invasion with pro-inflammatory cytokine exposure. The use of glucocorticoids such as methylprednisolone (1gr per day for 5 days), intravenous immunoglobulin (2gr per kilo) and even plasmapheresis is under review, but patients seem to be responders probably explained by an inflammatory mechanism as outlined previously.[9,21] This was the case with our patient that did respond to the immunomodulatory therapy. For refractory cases or with severe symptoms or slow response to the immunomodulatory therapy, even with active COVID-19 infection, tocilizumab (for example 400mg intravenously for one time) maybe useful due to its role blocking IL-6 and its effects in the dysfunctioning BBB[22].

The use of anti- CD20 therapies such as Rituximab or ocrelizumab is recommended as part of the therapy for autoimmune encephalitis, especially for cases with surface autoantibodies such as anti-NMDA receptor[23] but they should be put on hold during the active or recent COVID-19 infection. Data from registries[24,25] of patients using these therapies chronically showed that they are at increased risk of developing severe outcomes from COVID-19 with risk ratios ranging from 1.7 to 5.5. These therapies deplete B lymphocytes with a preservation of the T lymphocytes; the question raises if whether cellular immunity (T-lymphocytes) in the absence of humoral immunity (B-lymphocytes) is sufficient to protect against severe COVID-19[23]. On the other hand, with COVID-19 infection patients experiment lymphopenia with a marked decrease of the T lymphocytes[26] with increases the risk of a more severe disease or even the presence of other infections. The use of Rituximab for COVID-19 immune mediated encephalopathy should be considered as an alternative therapy when tocilizumab has failed[27] but in patients that normal lymphocyte counts and without active COVID-19 disease, since it is an effective therapy for antibody mediated encephalopathies[23].

The prognosis of this disease is variable depending on the patient. In the short term, an increase in mortality up to four times is observed in elderly patients. In the long term, there is an increase in 30-day mortality after hospitalization up to three times.[28] The most important factor is to be highly suspicious of the CNS involvement and the quick administrations of the immunomodulatory therapy. Guasp *et al.* [11] suggested that neuronal damage markers, and not pro-inflammatory cytokines predicts the long-term functional outcome in these patients, but these remains only in the investigation field and remains to be proven.

Conclusion

COVID-19-related encephalopathy is a common complication, that can present in a myriad of forms. Its diagnosis must be accompanied by a plausible temporal relationship, and other causes must be excluded. Brain MRI, EEG, lumbar puncture, and autoantibody tests are recommended. IVIG therapy, plasmapheresis, and immunosuppressants in severe cases can provide an optimal response; however, further studies are required to establish a protocol of treatment. The actual understanding of its physiopathological mechanisms can foster the development of new target-specific therapies, which can be useful in a COVID endemic state.

Funding: none

Conflict of interest: authors declare to have no conflict of interest regarding this topic

References

1. Ariño H, Heartshorne R, Michael BD, et al. Neuroimmune disorders in COVID-19. *J Neurol*. 2022;269(6):2827-2839. doi:10.1007/s00415-022-11050-w
2. Michael BD, Walton D, Westenberg E, et al. Consensus Clinical Guidance for Diagnosis and Management of Adult COVID-19 Encephalopathy Patients. *J Neuropsychiatry Clin Neurosci*. 2022; appineuropsych22010002. doi:10.1176/appi.neuropsych.22010002
3. Siahaan YMT, Puspitasari V, Pangestu A. COVID-19-Associated Encephalopathy: Systematic Review of Case Reports. *J Clin Neurol*. 2022;18(2):194-206. doi:10.3988/jcn.2022.18.2.194
4. Beghi E, Michael BD, Solomon T, Westenberg E, Winkler AS; COVID-19 Neuro Research Coalition. Approaches to understanding COVID-19 and its neurological associations. *Ann Neurol*. 2021;89(6):1059-1067. doi:10.1002/ana.26076
5. Ousseiran ZH, Fares Y, Chamoun WT. Neurological manifestations of COVID-19: a systematic review and detailed comprehension. *Int J Neurosci*. 2021;1-16. doi:10.1080/00207454.2021.1973000
6. Udzik J, Jakubowski P, Niekrasz M, Barczyszyn A, Parczewski M. COVID-19-Associated Encephalopathy-Case Series and Clinical Considerations. *J Clin Med*. 2022;11(4):981. doi:10.3390/jcm11040981
7. Shimohata T. Neuro-COVID-19. *Clin Exp Neuroimmunol*. 2022;13(1):17-23. doi:10.1111/cen3.12676
8. Katzourakis A. COVID-19: endemic doesn't mean harmless. *Nature*. 2022;601(7894):485. doi:10.1038/d41586-022-00155-x
9. Vanderheiden A, Klein RS. Neuroinflammation and COVID-19. *Curr Opin Neurobiol*. 2022;76:102608. doi:10.1016/j.conb.2022.102608
10. Alexopoulos H, Magira E, Bitzogli K, et al. Anti-SARS-CoV-2 antibodies in the CSF, blood-brain barrier dysfunction, and neurological outcome: Studies in 8 stuporous and comatose patients. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(6):e893. doi:10.1212/NXI.0000000000000893
11. Guasp M, Muñoz-Sánchez G, Martínez-Hernández E, et al. CSF Biomarkers in COVID-19 Associated Encephalopathy and Encephalitis Predict Long-Term Outcome. *Front Immunol*. 2022;13:866153. doi:10.3389/fimmu.2022.866153
12. Mondal R, Ganguly U, Deb S, et al. Meningoencephalitis associated with COVID-19: a systematic review. *J Neurovirol*. 2021;27(1):12-25. doi:10.1007/s13365-020-00923-3
13. Liotta EM, Batra A, Clark JR, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. *Ann Clin Transl Neurol*. 2020;7(11):2221-2230. doi:10.1002/acn3.51210
14. Kennedy M, Helfand BKI, Gou RY, et al. Delirium in Older Patients With COVID-19 Presenting to the Emergency Department. *JAMA Netw Open*. 2020;3(11):e2029540. doi:10.1001/jamanetworkopen.2020.29540
15. Helms J, Kremer S, Merdji H, et al. Delirium and encephalopathy in severe COVID-19: a cohort analysis of ICU patients. *Crit Care*. 2020;24(1):491. doi:10.1186/s13054-020-03200-1
16. Ladopoulos T, Zand R, Shahjouei S, et al. COVID-19: Neuroimaging Features of a Pandemic. *J Neuroimaging*. 2021;31(2):228-243. doi:10.1111/jon.12819
17. Gulko E, Oleksk ML, Gomes W, et al. MRI Brain Findings in 126 Patients with COVID-19: Initial Observations from a Descriptive Literature Review. *AJNR Am J Neuroradiol*. 2020;41(12):2199-2203. doi:10.3174/ajnr.A6805
18. Canham LJW, Staniaszek LE, Mortimer AM, Nouri LF, Kane NM. Electroencephalographic (EEG) features of encephalopathy in the setting of Covid-19: A case series. *Clin Neurophysiol Pract*. 2020;5:199-205. doi:10.1016/j.cnp.2020.06.001
19. Lewis A, Frontera J, Placantonakis DG, et al. Cerebrospinal fluid in COVID-19: A systematic review of the literature. *J Neurol Sci*. 2021;421:117316. doi:10.1016/j.jns.2021.117316
20. Wang H. COVID-19, Anti-NMDA Receptor Encephalitis and MicroRNA. *Front Immunol*. 2022;13:825103.. doi:10.3389/fimmu.2022.825103
21. Cao A, Rohaut B, Le Guennec L, et al. Severe COVID-19-related encephalitis can respond to immunotherapy. *Brain*. 2020;143(12):e102. doi:10.1093/brain/awaa337
22. Muccioli L, Pensato U, Cani I, et al. COVID-19-related encephalopathy presenting with aphasia resolving following tocilizumab treatment. *J Neuroimmunol*. 2020;349:577400. doi:10.1016/j.jneuroim.2020.577400

23. Franziska S. Thaler, Luise Zimmermann, Stefan Kammermeier et al. Rituximab Treatment and Long-term Outcome of Patients With Autoimmune Encephalitis. Real-world Evidence From the GENERATE Registry. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(6):e1088. doi: 10.1212/NXI.0000000000001088
24. Simpson-Yap S, De Brouwer E, Kalincik T et al. Associations of Disease-Modifying Therapies With COVID-19 Severity in Multiple Sclerosis. *Neurology*. 2021;97(19):e1870-e1885. doi: 10.1212/WNL.0000000000012753.
25. Andersen KM, Bates BA, Rashidi ES et al. Long-term use of immunosuppressive medicines and in-hospital COVID-19 outcomes: a retrospective cohort study using data from the National COVID Cohort Collaborative. *Lancet Rheumatol*. 2022;4(1):e33-e41. doi: 10.1016/S2665-9913(21)00325-8.
26. Tavakolpour S, Rakhshandehroo T, Wei EX, Rashidian M. Lymphopenia during the COVID-19 infection: What it shows and what can be learned. *Immunol Lett*. 2020;225:31-32. doi: 10.1016/j.imlet.2020.06.013.
27. Marengoni A, Zucchelli A, Grande G, Fratiglioni L, Rizzuto D. The impact of delirium on outcomes for older adults hospitalised with COVID-19. *Age Ageing*. 2020;49(6):923-926. doi:10.1093/ageing/afaa189