pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2022;18(1):102-104 / https://doi.org/10.3988/jcn.2022.18.1.102

Comments on "CSF-Confirmed SARS-CoV-2 Acute Encephalitis": SARS-CoV-2-Associated Encephalitis Is Autoimmune Rather Than Infectious

Josef Finsterer[a]
Fulvio Alexandre Scorza[b]
Ana Claudia Fiorini[c]

[a]Klinik Landstrasse, Messerli Institute, Vienna, Austria
[b]Disciplina de Neurociência, Escola Paulista de Medicina/Universidade Federal de São Paulo (EPM/UNIFESP), São Paulo, Brazil
[c]Programa de Estudos Pós-Graduado em Fonoaudiologia, Pontifícia Universidade Católica de São Paulo (PUC-SP), São Paulo, Brazil; Departamento de Fonoaudiologia, Escola Paulista de Medicina/Universidade Federal de São Paulo (EPM/UNIFESP), São Paulo, Brazil

Received July 6, 2021
Revised October 12, 2021
Accepted October 12, 2021

Correspondence
Josef Finsterer, MD, PhD
Klinik Landstrasse, Messerli Institute, Postfach 20, 1180 Vienna, Austria
Tel +43-1-71165
Fax +43-1-71165
E-mail fifigs1@yahoo.de

Dear Editor,

With interest we read the article by Tee et al.[1] about a 69-year-old male with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated encephalitis classified as infectious upon confirmation of the virus in the cerebrospinal fluid (CSF) by PCR. The patient benefited significantly from ceftriaxone, meropenem, favipiravir, dexamethasone, methylprednisolone, clonazepam, valproic acid, and tuberculostatics.[1] Complete recovery was achieved 10 days after the onset of the neurological compromise.[1] The study results are appealing, but they raise several comments and concerns, as detailed below.

One serious limitation of the study report is that reference limits for blood and CSF parameters were not provided, which greatly impedes the ability to interpret the results. According to our own laboratory, a cycle threshold of 36.08 for the CSF PCR is normal and does not prove infectivity. Thus, based on the study results, the diagnosis of infectious encephalitis due to infection with SARS-CoV-2 remains unproven.

Another limitation is that "results of other CSF analyses" were not specified.[1] It should be reported if investigations for viruses other than SARS-CoV-2 in the CSF were truly negative, if tuberculous meningitis and immune encephalitis were appropriately excluded, and if the CSF was tested for antibodies associated with immune encephalitis. Excluding immune encephalitis is crucial since SARS-CoV-2-associated encephalitis is due to an immune reaction against the virus rather than to a direct viral attack against the central nervous system.[2] Moreover, recovery under steroids suggests immune encephalitis rather than infectious encephalitis. Virostatics are usually ineffective against COVID-19. A further argument for an immune mechanism is that most of the patients with SARS-CoV-2-associated encephalitis were pathophysiologically classified as autoimmune (Table 1). However, in several cases encephalitis was classified as infectious despite the virus not being reported in the CSF. Though the absence of the virus in the CSF does not generally exclude an infectious pathomechanism, it does make it rather unlikely.

A further limitation is that cerebral magnetic resonance imaging (MRI) was not performed on admission. Encephalitis can usually be confirmed on T1-weighted images after administering gadolinium, by the presence of various degrees of focal or global enhancement. MRI performed 1 month after presentation will not reflect the acute disease. Additionally, fluorodeoxyglucose positron-emission tomography may show hypermetabolism within affected areas.[3] Several other cases of SARS-CoV-2-associated infectious encephalitis reported in the literature[4,5] were not listed in the table of the case report.[1]

We do not agree that the case reported by Duong et al.[6] can be classified as infectious encephalitis, since the presence of the virus could not be confirmed in that particular case. A comprehensive workup of the CSF, including a cytokine profile, was also missing. In particu-

Table 1. Selection of patients with SARS-CoV-2-associated infectious/autoimmune encephalitis

Age (yr)	Sex	CSFpos	TypeE	Reference
69	m	Equivocal	Equivocal	Tee et al.[1]
24	m	Yes	Infectious	Moriguchi et al.[9]
31	m	Yes	Infectious	Kamal et al.[10]
41	m	Yes	Infectious	Luis et al.[4]
25	f	Yes	Infectious	Luis et al.[4]
3	m	Yes	Infectious	Cheraghali et al.[5]
13	f	No	Infectious	Natarajan et al.[11]
11	m	No	Infectious	McAbee et al.[12]
52	m	No	Infectious	Lozano Gómez et al.[13]
70	m	No	Infectious	Lozano Gómez et al.[13]
41	f	No	Equivocal	Duong et al.[6]
69	m	No	Equivocal	Chaumont et al.[14]
5	f	No	Equivocal	Siracusa et al.[15]
56	m	No	Autoimmune	Parnasa et al.[16]
49	f	No	Autoimmune	Gunawardhana et al.[17]
44	f	No	Autoimmune	Dyachenko et al.[18]
43	f	No	Autoimmune	Vazquez-Guevara et al.[19]
31	m	No	Autoimmune	Jeanneret et al[20]
1	f	No	Autoimmune	Burr et al.[21]
8	m	No	Autoimmune	Abdel-Mannan et al.[22]
9	m	No	Autoimmune	Abdel-Mannan et al.[22]
31	f	No	Autoimmune	Benameur et al.[23]
64	m	No	Autoimmune	Benameur et al.[23]
34	m	No	Autoimmune	Benameur et al.[23]
40	f	No	Autoimmune	Tiraboschi et al.[3]
90	f	No	Autoimmune	Lv et al.[2]
36	m	No	Autoimmune	Miqdad et al.[24]
18	f	No	Autoimmune	Allahyari et al.[25]

CSFpos, CSF PCR positive for SARS-CoV-2; f, female; m, male; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TypeE, type of encephalitis.

lar, interleukin (IL)-8, IL-6, IL-1b, and tumor necrosis factor-alpha can be elevated in the CSF of patients with SARS-CoV-2-associated encephalitis or myelitis.[7,8]

In summary, the study of Tee et al.[1] has several limitations that challenge the reported results and their interpretation. The reported diagnosis of infectious encephalitis remains unproven, with the beneficial effect of steroids instead suggesting an autoimmune pathogenesis. Inflammatory cytokines should be measured in the CSF, which may reveal the immunological pathogenesis of SARS-CoV-2-associated encephalitis.

Ethics Statement

Not applicable

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

ORCID iDs

Josef Finsterer https://orcid.org/0000-0003-2839-7305
Fulvio Alexandre Scorza https://orcid.org/0000-0002-0694-8674
Ana Claudia Fiorini https://orcid.org/0000-0003-2989-2308

Author Contributions

Conceptualization: Josef Finsterer, Fulvio Alexandre Scorza. Data curation: Josef Finsterer. Investigation: Josef Finsterer. Methodology: Josef Finsterer, Fulvio Alexandre Scorza. Software: Josef Finsterer, Ana Claudia Fiorini. Supervision: Josef Finsterer. Visualization: Josef Finsterer. Writing—original draft: Josef Finsterer. Writing—review & editing: all authors.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

None

REFERENCES

1. Tee TY, Thabit AAM, Khoo CS, Shahrom HM, Chan EZ, Marzukie MM, et al. Acute encephalitis associated with SARS-CoV-2 confirmed in cerebrospinal fluid: first case in Malaysia. *J Clin Neurol* 2021;17:490-492.
2. Lv P, Peng F, Zhang Y, Zhang L, Li N, Sun L, et al. COVID-19-associated meningoencephalitis: a care report and literature review. *Exp Ther Med* 2021;21:362.
3. Tiraboschi P, Xhani R, Zerbi SM, Corso A, Martinelli I, Fusi L, et al. Postinfectious neurologic complications in COVID-19: a complex case report. *J Nucl Med* 2021;62:1171-1176.
4. Luis MB, Liguori NF, López PA, Alonso R. SARS-CoV-2 RNA detection in cerebrospinal fluid: presentation of two cases and review of literature. *Brain Behav Immun Health* 2021;15:100282.
5. Cheraghali F, Tahamtan A, Hosseini SA, Gharib MH, Moradi A, Razavi Nikoo H, et al. Case report: detection of SARS-CoV-2 from cerebrospinal fluid in a 34-month-old child with encephalitis. *Front Pediatr* 2021;9:565778.
6. Duong L, Xu P, Liu A. Meningoencephalitis without respiratory failure in a young female patient with COVID-19 infection in Downtown Los Angeles, early April 2020. *Brain Behav Immun* 2020;87:33.
7. Pilotto A, Masciocchi S, Volonghi I, De Giuli V, Caprioli F, Mariotto S, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) encephalitis is a cytokine release syndrome: evidences from cerebrospinal fluid analyses. *Clin Infect Dis* 2021;73:e3019-e3026.
8. Taghiloo S, Soltanshahi M, Aliyali M, Abedi S, Mehravaran H, Ajami A, et al. Cytokine profiling in Iranian patients with COVID-19; association with clinical severity. *Iran J Immunol* 2021;18:54-64.
9. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis* 2020;94:55-58.
10. Kamal YM, Abdelmajid Y, Al Madani AAR. Cerebrospinal fluid confirmed COVID-19-associated encephalitis treated successfully. *BMJ Case Rep* 2020;13:e237378.
11. Natarajan S, Ganesh R, Palaniappan N, Kannan L. SARS-CoV-2 encephalitis in an adolescent girl. *Indian Pediatr* 2020;57:1186-1187.
12. McAbee GN, Brosgol Y, Pavlakis S, Agha R, Gaffoor M. Encephalitis associated with COVID-19 infection in an 11-year-old child. *Pediatr Neurol* 2020;109:94.
13. Lozano Gómez H, Pascual Bielsa A, Abansés Moreno P, Luque Gómez MP, Matute Guerrero A, Araiz Burdio JJ. Encephalitis as a neurological manifestation of COVID-19. *Med Clin (Barc)* 2021;157:141-143.
14. Chaumont H, Etienne P, Roze E, Couratier C, Roger PM, Lannuzel A. Acute meningoencephalitis in a patient with COVID-19. *Rev Neurol (Paris)* 2020;176:519-521.

15. Siracusa L, Cascio A, Giordano S, Medaglia AA, Restivo GA, Pirrone I, et al. Neurological complications in pediatric patients with SARS-CoV-2 infection: a systematic review of the literature. *Ital J Pediatr* 2021;47:123.
16. Parnasa E, Kupietzky A, Korem M, Daana M. Autoimmune encephalitis secondary to COVID-19 infection. *Isr Med Assoc J* 2021;23:335.
17. Gunawardhana C, Nanayakkara G, Gamage D, Withanage I, Bandara M, Siriwimala C, et al. Delayed presentation of postinfectious encephalitis associated with SARS-CoV-2 infection: a case report. *Neurol Sci* 2021;42:3527-3530.
18. Dyachenko PA, Smiianova OI, Dyachenko AG. Meningo-encephalitis in a middle-aged woman hospitalized for COVID-19. *Wiad Lek* 2021;74:1274-1276.
19. Vazquez-Guevara D, Badial-Ochoa S, Caceres-Rajo KM, Rodriguez-Leyva I. Catatonic syndrome as the presentation of encephalitis in association with COVID-19. *BMJ Case Rep* 2021;14:e240550.
20. Jeanneret V, Winkel D, Risman A, Shi H, Gombolay G. Post-infectious rhombencephalitis after coronavirus-19 infection: a case report and literature review. *J Neuroimmunol* 2021;357:577623.
21. Burr T, Barton C, Doll E, Lakhotia A, Sweeney M. N-methyl-d-aspartate receptor encephalitis associated with COVID-19 infection in a toddler. *Pediatr Neurol* 2021;114:75-76.
22. Abdel-Mannan O, Eyre M, Löbel U, Bamford A, Eltze C, Hameed B, et al. Neurologic and radiographic findings associated with COVID-19 infection in children. *JAMA Neurol* 2020;77:1440-1445.
23. Benameur K, Agarwal A, Auld SC, Butters MP, Webster AS, Ozturk T, et al. Encephalopathy and encephalitis associated with cerebrospinal fluid cytokine alterations and coronavirus disease, Atlanta, Georgia, USA, 2020. *Emerg Infect Dis* 2020;26:2016-2021.
24. Miqdad MA, Enabi S, Alshurem M, Al-Musawi T, Alamri A. COVID-19-induced encephalitis: a case report of a rare presentation with a prolonged electroencephalogram. *Cureus* 2021;13:e14476.
25. Allahyari F, Hosseinzadeh R, Nejad JH, Heiat M, Ranjbar R. A case report of simultaneous autoimmune and COVID-19 encephalitis. *J Neurovirol* 2021;27:504-506.