



Commentary

The diagnosis of SARS-CoV-2 associated ADEM requires the exclusion of all differential diagnoses

ARTICLE INFO

Keywords

COVID-19

SARS-CoV-2

Febrile seizures

CNS complication

We read with interest the article by Ismaeili et al. about a 67 years-old male who developed impaired consciousness starting two days prior to admission [1]. The nasopharyngeal swab test was positive for SARS-CoV-2 but lung-CT was non-informative. Cerebral magnetic resonance imaging (MRI) on admission revealed extensive T2/FLAIR hyperintense lesions supra- and infra-tentorially, which only slightly enhanced [1]. Cerebro-spinal fluid (CSF) investigations were non-informative [1]. Acute, disseminated, encephalomyelitis (ADEM) was diagnosed [1]. On hospital day 2 COVID-19 pneumonia developed requiring mechanical ventilation [1]. Steroids and intravenous immunoglobulins (IVIG) were ineffective regarding ADEM and the patient died four weeks after admission due to worsening of the neurological and the pulmonary compromise [1]. The study is valuable but raises concerns that require discussion.

We do not agree with the diagnosis ADEM. Arguments against ADEM are that the CSF investigations were completely normal, that steroids and IVIG were ineffective, and that various differentials have not been adequately excluded. Differentials not excluded were HIV, tuberculosis, vasculitis, ischemic stroke, lymphoma, Whipple disease, sarcoidosis, disruption of the blood brain barrier, and venous thrombosis. Missing in this respect is the application of a multimodal MRI with diffusion weighted images (DWI), apparent diffusion coefficient (ADC) maps, perfusion weighted images (PWI), susceptibility weighted images (SWI), and the MRI angiography. T2 and FLAIR images are not sufficient to elucidate the nature of the CNS abnormalities. Missing is also the repetition of CSF investigations during the four weeks of hospitalisation to eventually detect CSF changes over time. We should be also told which neurological manifestations worsened during the four weeks, as indicated in the case description, and how this worsening was diagnosed. Has the cerebral MRI been repeated?

Extra-pulmonary onset of COVID-19 is not unusual. In a recent review about the extra-pulmonary onset of COVID-19 a number of central nervous system (CNS) disorders were reported, such as headache, ischemic stroke, epilepsy, intracerebral bleeding, delirium, confusion,

altered mental state, memory impairment, transverse myelitis, and ADEM [2]. COVID-19 may not only start with CNS disease but also with peripheral nervous system (PNS) abnormalities, such as hyposmia, hypogeusia, Guillain-Barre syndrome, peripheral facial palsy, myositis, or rhabdomyolysis [2]. Extra-pulmonary onset of COVID-19 has been also reported in the eyes, ears, heart, intestines, arteries, veins, skin, and blood [2].

ADEM as the initial clinical manifestation of a SARS-CoV-2 infections is not unusual. ADEM as the onset manifestation of COVID-19 has been reported by Abdi et al. and by Wang et al. [3,4]. Abdi et al. reported a 58 years-old male who developed gait disturbance and impaired consciousness starting one month prior to admission [3]. MRI showed the typical features of ADEM. Nasopharyngeal and oropharyngeal swab real-time polymerase chain reaction (rt-PCR) were positive for SARS-CoV-2 virus but negative in the CSF [3]. The patient profited significantly from steroids [3]. Wang et al. reported six patients who did not present with any symptoms prior to onset of ADEM and several patients in whom the initial manifestations were not provided [4].

Overall, the interesting study has limitations and inconsistencies that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could add value to the study. As long as differential causes of the described cerebral lesions had not been appropriately excluded, ADEM remains an unconfirmed diagnosis.

Sources of funding

Funding sources: no funding was received.

Ethics approval

Was in accordance with ethical guidelines. The study was approved by the institutional review board.

Consent to participate: was obtained from the patient.

Abbreviations: ADEM, acute disseminated encephalomyelitis; ADC, apparent diffusion coefficient; COVID, coronavirus disease; CSF, cerebrospinal fluid; CT, computed tomography; DWI, diffusion weighted images; FLAIR, fluid attenuated inversion recovery; IVIG, intravenous immunoglobulins; PWI, perfusion weighted images; SARS-CoV-2, severe, acquired respiratory syndrome coronavirus-2; SWI, susceptibility weighted images.

<https://doi.org/10.1016/j.amsu.2022.103662>

Received 12 April 2022; Accepted 18 April 2022

Available online 22 April 2022

2049-0801/© 2022 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Consent for publication: was obtained from the patient.

Consent

Not applicable.

Availability of data

All data are available from the corresponding author.

Code availability

Not applicable.

Trial registry number

Name of the registry:

Unique Identifying number or registration ID:

Hyperlink to your specific registration (must be publicly accessible and will be checked):

Guarantor

Not applicable.

Author contributions

JF: design, literature search, discussion, first draft, critical comments, final approval, FS: literature search, discussion, critical comments, final approval.

Declaration of competing interest

None.

Acknowledgement

None.

References

- [1] S. Esmaili, M.H. Abbasi, M.T. Joghataei, Z. Mirzaasgari, M. Emamikhah, M. J. Makiani, H. Nazarian, Acute disseminated encephalitis (ADEM) as the first presentation of COVID-19; a case report, *Ann. Med. Surg. (Lond)*. 77 (2022 Mar 28) 103511, <https://doi.org/10.1016/j.amsu.2022.103511>.
- [2] J. Finsterer, F.A. Scorza, C.A. Scorza, A.C. Fiorini, Extrapulmonary onset manifestations of COVID-19, *Clinics* 76 (2021 Jul 5), e2900, <https://doi.org/10.6061/clinics/2021/e2900>. PMID: 34231709; PMCID: PMC8240766.
- [3] S. Abdi, A. Ghorbani, F. Fatehi, The association of SARS-CoV-2 infection and acute disseminated encephalomyelitis without prominent clinical pulmonary symptoms, *J. Neurol. Sci.* 416 (2020 Sep 15) 117001, <https://doi.org/10.1016/j.jns.2020.117001>.
- [4] Y. Wang, Y. Wang, L. Huo, Q. Li, J. Chen, H. Wang, SARS-CoV-2-associated acute disseminated encephalomyelitis: a systematic review of the literature, *J. Neurol.* 269 (3) (2022 Mar) 1071–1092, <https://doi.org/10.1007/s00415-021-10771-8>.

Josef Finsterer*

Neurology & Neurophysiology Center, Vienna, Austria

Fulvio A. Scorza

Disciplina de Neurociência, Universidade Federal de São Paulo/Escola

Paulista de Medicina (UNIFESP/EPM), São Paulo, Brazil

E-mail addresses: scorza@unifesp.br, carlascorza.nexp@gmail.com.

* Corresponding author. Postfach 20, 1180, Vienna, Austria.

E-mail address: fifigs1@yahoo.de (J. Finsterer).