Int. j. adv. multidisc. res. stud. 2022; 2(3):402-403

Received: 28-05-2022
Accepted: 04-06-2022

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Letter to the Editor

Diagnosing SARS-CoV-2 encephalitis requires evidence

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We eagerly read the article by Handa *et al*. about a 46 years old male who was admitted for SARS-CoV-2 associated encephalitis diagnosed upon fever, altered mental status, a Glasgow Coma score (GCS) of E2V3M4, and an RT-PCR positive for SARS-CoV-2 on hospital day 3 [1]. The patient was intubated and mechanically ventilated [1]. Work-up for encephalitis revealed T2-, fluid attenuated inversion recovery (FLAIR), and diffusion weighted imaging (DWI) hyperintense lesions in the left frontal lobe, both insula, and the medial left temporal lobe [1]. There was aseptic pleocytosis of 54/3 cells [1]. Despite application of acyclovir, ceftriaxone, levetiracetam, and steroids the patient died 10 days after admission [1]. The study is appealing but raises concerns that require discussion.

We do not agree with the diagnosis SARS-CoV-2 encephalitis [1]. The cerebrospinal fluid (CSF) was not investigated for SARS-CoV-2, neither intra vitam nor at autopsy. Therefore, the diagnosis SARS.CoV-2 encephalitis is not supported by evidence but remains speculative. A strong argument against SARS-CoV-2 associated encephalitis is that the RT-PCR for SARS-CoV-2 was negative on admission, suggesting that the central nervous system (CNS) compromise, which began one week prior to admission, was unrelated to SARS-CoV-2 [1].

A limitation of the study is that no contrast medium was applied [1]. Cerebral lesions of encephalitis can be enhancing on MRI. Application of contrast medium is also required to exclude certain differentials. Further limitations of the study are that no MRI of the spinal cord and no magnetic resonance angiography (MRA) respectively black blood sequences had been carried out. Apparent diffusion coefficient (ADC) maps are missing to assess if DWI hyperintensities represented a cytotoxic or a vasogenic edema.

A severe limitation of the study is that various differentials of infectious encephalitis were not appropriately excluded. These differentials include acute, disseminated encephalomyelitis (ADEM), acute, hemorrhagic, necrotising encephalitis (AHNE), immune encephalitis, HIV, tuberculosis, cerebral vasculitis, and lymphoma. Lymphoma should have been excluded by application of contrast medium. Tuberculosis should have been excluded by PCR for mycobacterium tuberculosis. HIV should have been excluded by performing a PCR for HIV. Exclusion of autoimmune encephalitis requires determination of autoimmune encephalitis antibodies [2]. Diagnosing vasculitis requires determination of vasculitic parameters and MRA.

Another limitation is that the cytokine and chemokine profiles were not determined in the CSF. Interleukine (IL) 6, IL-8, TNF-alpha, and IL-1b have been shown elevated in SARS-CoV-2 associated CNS disease [3].

It is unclear why the patient received levetiracetam (LEV). There was no evidence for seizures and the electroencephalography (EEG) was normal [1]. LEV has side effects [4] and should be applied only when indicated.

Overall, the elegant study has limitations which challenge the results and their interpretation. The shortcomings should be addressed to amend the results and to strengthen the conclusions. The diagnosis SARS-CoV-2 encephalitis is unsupported by evidence and remains a speculation.

Declarations
Funding sources: no funding was received.

Conflicts of interest: The authors declare no conflicts of interest.

Acknowledgement: none

Ethics approval: was in accordance with ethical guidelines. The study was approved by the institutional review board.

Keywords: SARS-CoV-2, COVID-19, Encephalitis, Complication, neuro-COVID

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