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SARS-CoV-2 related encephalitis requires documentation of the virus in the cerebrospinal fluid

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I read with interest the article by Yimenicioglu et al.[1] about a 15-year-old male who developed headache, malaise, vomiting, and loss of appetite one week prior to admission and additionally vertigo, clumsiness, and drop attacks three days prior to admission. Because he developed a coma one day after admission, he was intubated and mechanically ventilated[1]. The patient was diagnosed with encephalitis upon the clinical presentation and cerebral MRI, which showed cytotoxic edema in the fronto-temporal regions bilaterally[1]. Despite extensive work-up the cause of encephalitis could not be clarified and empiric treatment did not result in resolution of the abnormalities and the patient died[1]. The study is appealing but raises concerns that should be discussed.

The main limitation of the study is that a causal relationship was established without providing evidence for it. The patient had a SARS-CoV-2 infection five months prior to the onset of the neurological compromise, a latency too long to establish a causal relationship. Furthermore, a SARS-CoV-2 infection was not ruled out on admission[1] and it is not mentioned if the index patient had undergone anti-SARS-CoV-2 vaccination or not. It is unclear if mentioning a positive PCR for SARS-CoV-2 in the discussion refers to the infection five months before admission or the current admission.

A further strong limitation of the study is that no autopsy had been carried out to prove or disprove SARS-CoV-2 associated encephalitis.

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A third limitation is that no cerebrospinal fluid (CSF) investigations had been carried out to prove or disprove the diagnosis of encephalitis. Encephalitis cannot be diagnosed upon imaging alone but requires documentation of the infectious agents causing encephalitis in the CSF. Imaging is only a supportive diagnostic tool.

Furthermore, differential diagnoses of cytotoxic edema were not sufficiently considered. The most common differential diagnosis characterized by a cytotoxic edema is ischemic stroke. Because ischemic stroke can be a complication of venous sinus thrombosis (VST), because the D-dimer was elevated, and because VST can be a complication of SARS-CoV-2 infections[2], it is crucial that VST had been appropriately ruled out by MR venography (MRV).

Missing are the levels of autoantibodies associated with immune encephalitis. There are an increasing number of reports showing that SARS-CoV-2 infections can trigger the development of antibody mediated autoimmune encephalitis.[3]

I disagree with the notion that a Glasgow Coma Scale (GCS) of 3 is a contraindication for lumbar puncture.[1] On the contrary, a coma is an indication for lumbar puncture if imaging or electroencephalography (EGG) do not sufficiently explain the cause of unconsciousness.

It is not comprehensible how the D-dimer could be elevated on hospital day three, although the patient had already died 48 hours after admission. This discrepancy should be explained.

No reference limits for blood tests were provided, which is why it is difficult to assess which parameters were truly elevated or normal.

Overall, the interesting study has some limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and improve the study. Diagnosing encephalitis requires CSF investigations and either confirmation of an infectious agent or documentation of elevated antibodies associated with immune encephalitis.

Key words: COVID-19, SARS-CoV-2, encephalitis, complication, brain, MRI.

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