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Letter to the Editor

Before NMDA-associated immune encephalitis is attributed to SARS-CoV-2, differential diagnoses must be ruled out

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We read with interest the article by Sanchez-Larsen *et al*. about a 22yo female diagnosed with N-methyl-D-aspartate (NMDA) antibody positive immune encephalitis, being attributed to an infection with SARS-CoV-2 [1]. The patient recovered completely upon application of anti-seizure drugs (ASDs), steroids, intravenous immunoglobulins (IVIG), and rituximab [1]. The study is appealing but raises concerns.

We disagree with the notion that NMDA-related immune encephalitis was due to the SARS-CoV-2 infection [1]. Because epilepsy can be the initial manifestation of an autoimmune encephalitis [2gole], it is conceivable that immune encephalitis had developed already before the SARS-CoV-2 infection at age 20y, when the first seizure occurred. It should be reported whether cerebrospinal fluid (CSF) investigations had been performed already at age 20y. We should also know how epilepsy was classified and treated at age 20.

There is no information about the results of the virus panels in the serum and CSF [1]. Because virus encephalitis can go along without pleocytosis and without a structural lesion on cerebral MRI, it is crucial to know if alternative viral triggers of encephalitis were appropriately ruled out.

A limitation is that the CSF was not tested for SARS-CoV-2 [1]. Because SARS-CoV-2 can trigger encephalitis [3turan], it is crucial to test the CSF with a PCR for SARS-CoV-2. It is conceivable that NMDA antibodies were present already prior to the current admission, and that SARS-CoV-2 was the actual trigger of encephalitis. Therefore, we should know if the CSF was tested for cytokine levels, glial markers, neurofilament light chain (NFL) which can be elevated in central nervous system involvement in a SARS-CoV-2 infection [4guasp].

A further limitation of the report is that the specific anti-seizure drugs (ASDs) were not provided [1]. To assess whether ASDs contributed to the neurological and psychiatric abnormalities described in the patient, it is crucial to know the compounds applied and their dosages.

We disagree with the statement that clinical manifestations of encephalitis were mild [1]. The patient had a series of four secondary generalised tonic clonic seizures, aphasia, and various psychiatric abnormalities [1].

There is no information whether an EEG was recorded after complete recovery and whether NMDA antibodies persisted beyond full recovery.

Of interest are the serum levels of neurtralising IgG and IgM antibodies and whether rituximab was given before or after full recovery.

Overall, the interesting study has limitations that challenge the results and their interpretation. Before blaming SARS-CoV-2 for autoimmune encephalitis, various differential causes need to be ruled out.

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