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Letter to the Editor

SARS-CoV-2-associated encephalitis has differential diagnoses

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We read with interest the article by Koupaei *et al.* about a systematic review about the clinical presentation, diagnosis, treatment, and outcome of SARS-CoV-2 associated encephalitis in 53 patients retrieved from various databases^[1]. It was found that 45% had white matter lesions, 17% temporal lobe lesions, 11% hemorrhages, that 36% received steroids, 28% intravenous immunoglobulines (IVIG), and 17% acyclovir. Twenty-eight percent of patients died^[1]. It was concluded that encephalitis occurs in severe COVID-19 cases and increases mortality^[1]. The study is attractive but raises concerns that should be discussed.

Surprisingly, only 46% of the included patients underwent cerebrospinal fluid (CSF) investigations^[1]. We shall be told how encephalitis can be diagnosed without analysis of the CSF. Bacterial meningitis can be ruled out only by CSF analysis. All patients without CSF analysis should have been excluded from the evaluation.

The cause of death among the 13/59 patients that died should be provided. Did these patients die from encephalitis or from involvement of the lungs? How many of those who died underwent autopsy and which was the result?

Missing is the information how many of the patients receiving cerebral imaging had received contrast medium. Cerebral MRI/CT without contrast medium may be insufficient to document a cerebral lesion. Furthermore, contrast enhancement may indicate inflammation.

Interestingly, 11% of the patients had some sort of intracerebral bleedings^[1]. We should be told if these patients fulfilled the diagnostic criteria for acute, haemorrhagic leucoencephalitis (AHLE) or acute, haemorrhagic, necrotising encephalitis (AHNE)?

The question whether there was a difference between pediatric and adult patients regarding clinical presentation, diagnosis, treatment, and outcome of SARS-CoV-2 associated encephalitis was not addressed.

We do not agree with the statement that headache is “a less common clinical manifestation of COVID-19”^[1]. On the contrary, headache is one of the most common neurological manifestations of SARS-CoV-2 infections and has been reported in the first report about the neurological implications of COVID-19 patients with a frequency of xx percent^[2]. The cause of headache in COVID-19 is multifactorial and can be due to increased tension of neck muscles, migraine, encephalitis, meningitis, increased intracerebral pressure, reversible cerebral vasoconstriction syndrome (RCVS), venous sinus thrombosis (VST), intracerebral bleeding (ICB), or subarachnoid bleeding (SAB)^[3].

Myelitis is a CNS inflammation. It is not comprehensible why myelitis was not classified as CNS inflammation^[1].

It is not comprehensible why articles published as of the 1st January 2019 were included. The pandemic and the reports about CNS involvement started not earlier than at the beginning of 2020. We should know why the search terms did not include “AHLE”, “AHNE”, and “meningo-encephalitis”? Several studies may have been missed if these terms were not included.

Important parameters not extracted from the dataset were the latency between onset of COVID-19 and onset of encephalitis, onset manifestations of encephalitis, if RT-PCR for SARS-CoV-2 was positive in the CSF or not, and if contrast medium was applied or not.

Overall, the interesting study has some limitations and inconsistencies that call the results and their interpretation into question. Addressing these limitations could further strengthen and reinforce the statement of the study. Rhabdomyolysis requires extensive work-up to uncover the underlying cause and to prevent recurrence. SARS-CoV-2 associated encephalitis needs to be confirmed by CSF analysis and cerebral imaging requires the application of contrast medium.

Keywords: SARS-CoV-2, COVID-19, Encephalitis, Central Nervous System, Vaccination, Side Effect, Adverse Reaction, Rhabdomyolysis

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