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Letter to the Editor

Calculating the Prevalence of NMDA-associated Encephalitis caused by COVID Infection/Vaccination Requires an Appropriately Designed Study

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We were interested to read the article by Vasilevska *et al*. on a systematic review of NMDA-associated autoimmune encephalitis (AIE) in 19 patients following SARS-CoV-2 infection (SC2I, n=16) or SARS-CoV-2 vaccination (SC2V, n=3) [1]. Four of these patients had an ovarian teratoma, which is known to be associated with NMDA-associated AIE. Whether the association between SC2I/SC2V and NMDA-associated AIE in the remaining patients was causal or coincidental remained speculative, as it was unclear whether the NMDA receptor antibodies were already present and entered the brain through SC2I- or SC2V-related blood-brain barrier leaks [1]. The study is excellent, but some points should be discussed.

The first point is that the review does not support the conclusion that SC2I or SC2V does not increase the prevalence of de novo NMDA-associated AIE [1]. Firstly, not all cases with NMDA-associated AIE have been published. Secondly, it cannot be ruled out that none of the patients already had NMDA receptor antibodies. Thirdly, not all cases with SC2I/SC2V-related AIE also had NMDA receptor antibodies. Fourth, only a prospective, multicenter study with a control group can assess whether the prevalence of SC2I/SC2V-associated NMDA-related AIE has actually increased during the pandemic.

A second point is that antibodies against the spike protein of the virus were not measured in the cerebrospinal fluid (CSF) of all 19 patients [1]. The detection of antibodies against the spike protein would confirm that the virus has entered the brain or that the vaccine RNA has entered the CSF.

The third point is that the search terms used for PubMed and Google Scholar searches did not include a keyword related to SC2V [1]. How were patients with NMDA-associated AIE after SC2V identified? How many patients with NMDA-associated AIE due to SC2V were missed?

The fourth point is that patients from a meta-analysis were included [1]. How can the authors be sure that the patients included in the meta-analysis were not also published as case reports and that therefore some of the patients were actually included twice?

The fifth point is that it was not defined according to which criteria NMDA-associated AIE was diagnosed. Did the diagnostic criteria require NMDA antibodies in CSF or only in serum? Did the diagnostic criteria require normal blood-brain barrier (BBB) function but NMDA receptor antibodies in the CSF? Did the diagnostic criteria require an enhancing lesion in the brain parenchyma, pleocytosis or elevated CSF protein or both? How was AIE diagnosed in the one patient with a normal cerebral CT scan?

The sixth point is that the minimum and maximum length of the interval between the occurrence of SC2I or the date of SC2V and the occurrence of AIE has not been defined [1]. We should know the minimum and maximum length of this interval, on the basis of which a causal relationship between SC2I/SC2V and AIE was assumed.

It is also unclear why three patients were included when not all data were available [1]. What kind of data was missing for these three patients? Why were these three patients included in the analysis? Missing data were also reported in patients 3, 6, 17 and 18 [1]. For how many patients did the authors obtain missing data by contacting the authors of the index study by telephone? It is also not understandable how the EEG can indicate subcortical dysfunction [1].

In conclusion, it can be said that this interesting study has limitations that relativize the results and their interpretation. Addressing these limitations could strengthen the conclusions and reinforce the message of the study. The prevalence of SC2I/SC2V-related NMDA-associated AIE can only be determined by a prospective, controlled multicentre study.

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