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Letter to the Editor

Whether Tocilizumab is Beneficial for SARS-CoV-2-associated Acute Necrotizing Encephalopathy Requires Appropriately Designed Studies

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We read with interest the article by Ma *et al*. on a case series of eight pediatric patients studied by the authors and 11 patients from the literature with acute necrotizing encephalopathy (ANE) due to SARS-CoV-2 infection (SC2I) [1]. Of the 19 patients, 18 had fever, 12 had impaired consciousness, and eight had seizures [1]. Of the eight patients at the investigating center, all had elevated procalcitonin, six had elevated alanine aminotransferase, and seven had elevated uric acid [1]. Cerebral imaging showed symmetrical lesions in the thalamus, cerebellum, basal ganglia, brainstem, and white matter [1]. Of the 19 patients, 8 died [1]. Those who received tocilizumab in addition to glucocorticoids had lower mortality than those who received steroids alone [1]. The study is excellent, but some points should be discussed.

The first point is that it is not possible to draw general conclusions about the treatment effect of a particular drug from a case series of eight or 19 patients. Prospective, randomized, double-blind, placebo-controlled, cross-over studies are required to assess the efficacy of a drug such as tocilizumab. As long as such studies are not available, only estimates, expert opinions, and speculations can be made. Furthermore, not all of the eight included patients also received tocilizumab [1]. According to Table 2, only two of the patients diagnosed by the authors and only four of the patients recruited from the literature had received tocilizumab. In addition, all six patients treated with tocilizumab also received other drugs, making it difficult to assess which of the drugs used were truly effective and which had no effect.

The second point is that the diagnostic criteria used to diagnose ANE are weak [1]. Elevated protein in the CSF is a non-specific finding, and it is also unclear how elevated CSF protein due to blood-brain barrier disruption was ruled out. As for the imaging criteria of ANE on cerebral CT and cerebral MRI, symmetrical lesions in the thalamus, tegmentum, brainstem, internal capsule, and basal ganglia, for example, are also seen in patients with Leigh syndrome [2]. We should therefore know whether Leigh syndrome was really excluded in all eight patients and by which examinations this was done. Leigh syndrome was not mentioned as an exclusion criterion [1]. It is also not reported how many of the five diagnostic criteria the eight patients had to fulfill before the diagnosis of ANE was made. For example, no CSF examination results are reported for patient-1 [1].

Thirdly, we disagree with the view that acute disseminated encephalomyelitis and encephalitis are similar diseases to ANE. In ADEM and encephalitis, the cerebral lesions are usually not symmetrically distributed.

The fourth point is that the mortality rate was high at 42% [1]. We should know whether these eight patients died from pulmonary complications of SC2I or whether they died from ANE or other non-pulmonary causes. It would also be interesting to know how many of the deceased underwent autopsy and whether the diagnosis of ANE was confirmed by autopsy in all of these eight patients. In particular, we should know whether the lesions detected on imaging at autopsy actually corresponded to necrosis.

The fifth point is that the latency period between the occurrence of SC2I and the occurrence of ANE has not been reported [1]. In order to assess whether there is indeed a causal relationship between SC2I and ANE, documentation of a close temporal relationship is imperative.

A sixth point is that there is no mention of how many of the included patients had a CCT and how many had an MRI and how many had both for cerebral imaging. We should also know how many of the patients who underwent an MRI had a multimodality MRI and how many received a contrast agent.

A seventh point is that the MRI lesions shown in Figure 1 are not symmetrical and therefore do not fulfill the diagnostic criteria. Why was patient 1 diagnosed with ANE even though he did not meet all diagnostic criteria?

In summary, 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 substantiate the study's message. There is a need to develop more efficient diagnostic criteria for ANE and to conduct appropriately designed studies to evaluate the effect of any drug, including tocilizumab.

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