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Letter to the Editor

Rule out alternative mechanisms before SARS-CoV-2 is held responsible for causing status epilepticus in Uverricht-Lundborg disease

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We read with interest the article by Kizilkilic *et al*. about a 21 years-old male with Uverricht-Lundborg disease (ULD) who developed refractory status epilepticus (SE) during mild infection with SARS-CoV-2 [1]. After several anti-seizure drugs (ASDs) failed to terminate SE, tocilizumab was tried with success [1]. It was concluded that tocilizumab can be considered as a treatment option in patients with SE and refractory seizures [1]. The report is attractive but raises concerns that should be discussed.

We disagree with the conclusion that tocilizumab "can be considered as a treatment option in patients with SE and refractory seizures" [1]. First, tocilizumab has not been approved as an ASD by any national or international epileptology society. Second, there are no reports in the literature of the anticonvulsant effect of tocilizumab. Third, the study design (case report) is unsuitable for assessing the general treatment effect of a drug. Sufficiently powered, randomised controlled trials are needed to assess whether tocilizumab really has antiepileptic potential.

We also disagree that "the mechanism of action by which SARS-CoV-2 causes SE is not known" [1]. SE has been reported as manifestation of multisystem inflammatory syndrome (MIS) [2]. of SARS-CoV-2 associated encephalopathy [3], and of SARS-CoV-2 associated meningo-encephalitis [4]. We should be told whether these conditions have been considered as alternative triggers for SE and ruled out accordingly.

Furthermore, we disagree with the assumption that SARS-CoV-2 was the cause of SE [1]. The index patient was treated with favipiravir two months before admission for SARS-CoV-2 infection [1]. Since drug-drug interactions between favipiravir and ASDs have been reported [5]. it cannot be ruled out that favipiravir use triggered SE by reducing serum levels of ASDs that the patient was taking prior to developing SE. We should be told for how long and at what dose favipiravir was administered and what ASDs the index patient was taking prior to SARS-CoV-2 infection. We should also be informed if the patient has received any medication other than favipiravir for the SARS-CoV-2 infection.

An argument against hyper-IL-6 emia as a trigger of SE is that many patients with epilepsy have been infected since the beginning of the pandemic and have responded with a cytokine storm, including elevated IL-6, but did not experience an increase in seizures frequency or severity.

The PCR for SARS-CoV-2 in the CSF and the cytokine, chemokine, and glial factor levels in the CSF were not reported. Since the authors suspected the immunologic reaction to be the cause of SE, documentation of the suspected causal immune reaction is required.

It is reported that ULS has been genetically confirmed in the index patient [1]. However, there is no mention of which variant was detected in the cystatin-B (CSTB) gene, whether the variant was known or new, and whether the variant occurred in a homozygous or compound heterozygous distribution.

Overall, the interesting study has some limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study. It remains questionable whether SARS-CoV-2 triggered SE in the index patient and whether tocilizumab stopped the SE.

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Keywords: COVID-19, SARS-CoV-2, Status Epilepticus, Tocilizumab, Cytokine Storm

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