Presence of Severe Acute Respiratory Syndrome Coronavirus 2 in the Cerebrospinal Fluid of Guillain-Barré Syndrome Patients Requires Validation

To the Editors:

With interest, we read the article by Araújo et al.1 about a 17-year-old female who was diagnosed with Guillain-Barré syndrome (GBS), and subtype acute, demyelinating inflammatory polyneuropathy, 8 days after onset of a mild coronavirus disease 2019 infection. Surprisingly, cerebrospinal fluid (CSF) investigations were positive for RNA of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).1 The patient profited from IV immunoglobulins.1 The study is appealing but raises concerns.

The main limitation is that the test upon which SARS-CoV-2 RNA was detected in the CSF was not specified. Although a control mock CSF tested negative for the virus, there is no mentioning if the applied test was validated for CSF testing. There is also no discussion about the possibility that the test was false positive. Sensitivity and specificity of the applied real-time polymerase chain reaction were not provided. No information about the test-retest reliability was provided.

There were also no repeated CSF investigations for the virus during follow-up, why it remains unknown for how long the virus could be proven in the CSF.

A second limitation is that there was no discussion about the pathophysiologic implications of the test result. Because GBS is an immunologic and not an infectious disorder, it is rather unlikely that presence of the virus in the CSF had a direct pathophysiologic consequence. Anyhow, presence of SARS-CoV-2 is not uncommon.

Particularly in patients experiencing meningitis or encephalitis, SARS-CoV-2 has been repeatedly found in the CSF.2,3 In immune-mediated complications of SARS-CoV-2, however, SARS-CoV-2 is usually absent in the CSF. In a study of 220 patients with SARS-CoV-2-associated GBS, collected until the end of December 2020, CSF was investigated for the virus in 56 cases but was found in none of them.4 Absence of the virus in the CSF was explained by the assumption that the virus never enters the CSF or that it enters the CSF but remains only for a short time before invading neurons or endothelial cells. An argument for the temporary presence of the virus in the CSF is that virus RNA has been found on autopsy studies in neurons and endothelial cells of the frontal lobe.6

There is also no discussion via which pathway the virus had entered the CSF. Speculations in the literature include retrograde migration of the virus along cranial or peripheral nerves, hematogenic spread, or intracellular transport in leukocytes via the blood–brain barrier.

Missing are the results of the cerebral magnetic resonance imaging with contrast medium. Because GBS can manifest as Bickerstaff encephalitis, it is crucial to know if there was immune encephalitis of the brainstem or not. In this respect, it should be mentioned if there was involvement of cranial nerves, the respiratory muscles or the bulbar muscles. Because GBS may be complicated by autonomic involvement, we should know if the patient ever developed autonomic dysfunction.

Although SARS-CoV-2-associated GBS is more prevalent in adults compared with children or adolescents, there is increasing evidence that also younger ages can be affected. In the study of 220 patients with SARS-CoV-2-associated GBS, 6 patients were below age 18 years.5 A shortcoming of Table 1 is that no reference limits were provided.

Overall, the interesting study has limitations which challenge the results and their interpretation. There is a need to address these limitations to strengthen the conclusions.

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with detection of SARS-CoV-2 in the cerebrospinal fluid (CSF). In this case, the Quick-DNA/RNA Viral MagBead (Zymo Research Corp, Irvine, CA) extraction kit on the automated KingFisher Flex Purification System (Thermo Fisher Scientific, Waltham, MA) was used for nucleic acid extraction and the Allplex nCoV-2019 kit (Seegene, Inc., Seoul, South Korea) for gene amplification. Moreover, appropriate positive, negative and internal controls were used to add confidence in the results. The multiplex real-time RT-PCR assay used in this case has a limit of detection of 4167 copies/ml and a sensitivity of 100 copies/reaction. Target genes amplified within ≤40 cycle threshold were considered detected, and the patient had a positive result for the presence of SARS-CoV-2 RNA in the CSF.

Regarding the possibility of repeating the CSF virus investigation during follow-up, we decided not to perform invasive procedures with exclusively academic purpose, as this would not change the therapeutic approach. In addition, brain magnetic resonance imaging (MRI) was normal and the patient did not show any signs of brain involvement suggestive of Bickerstaff encephalitis, such as external ophthalmoplegia or disturbance of consciousness. Respiratory muscles were not involved nor did the patient have autonomic dysfunction. The symptoms presented by the patients were explained in the article.

Finally, it is worth remembering that during the recent Zika and Chikungunya epidemics, viral RNA was also found in CSF of patients with Guillain-Barré syndrome, as well as the presence of IgM and IgG. According to Parra et al., arbivirus-related GBS may be caused by direct infection or parainfectious nerve damage, due to the short time between onset of infectious and neurologic symptoms. Although direct viral invasion is a less likely pathophysiological mechanism for a disease classically defined as immune-mediated, the presence of SARS-CoV-2 RNA in CSF makes it impossible for us to rule out this hypothesis.

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Remdesivir, Sinus Bradycardia and Therapeutic Drug Monitoring in Children With Severe COVID-19

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