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LETTER TO THE EDITOR

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Comment on "Encephalopathy in patients with COVID-19: A review"

To The Editor,

I read with great interest the article by Garg et al[1] on "Encephalopathy in patients with COVID-19: A review." The authors performed a review of published reports on coronavirus disease-2019 (COVID-19)-associated encephalitis and encephalopathy. They are to be congratulated for their timely, comprehensive, and insightful paper. Several aspects of cerebrospinal fluid analysis in patients with COVID-19 having neurological manifestations, however, need to be further discussed.

First, reliable cerebrospinal fluid (CSF) biomarkers to confirm the involvement of the central nervous system (CNS) in COVID-19 are still lacking. Previous reports, which mainly focused on the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA in CSF samples of patients with COVID-19 having neurological manifestations using reverse transcriptase-polymerase chain reaction (RT-PCR) tests, have reported inconsistent results. The majority of the studies have reported negative findings,[2-6] whereas some have successfully detected SARS-CoV-2 RNA in CSF.[7,8] These SARS-CoV-2 CSF PCR results should be interpreted with caution due to several reasons. The results were mainly based on case reports and case series, which may compromise on generalization. Also, the dynamics of SARS-CoV-2 in CSF are not fully understood and hence, no validated CSF assays are currently available. Furthermore, there are concerns about "false negative" SARS-CoV-2 PCR results, which have been observed to occur in up to 40% of throat sample tests.[9] As such, a negative RT-PCR may not necessarily mean that SARS-CoV-2 is absent in the CSF. High-quality studies that are adequately powered to address these issues are urgently needed.

Second, whereas lack of identification of SARS-CoV-2 RNA in CSF may be indicative of the limitations of the currently available tests, it may also mean that the neurological manifestations could be mediated indirectly, through immune-related mechanisms. It is noteworthy that most of the above studies did not provide data on anti-SARS-CoV-2 antibodies within the CSF. Recently, several studies have successfully demonstrated the presence of these antibodies in the CSF of patients with COVID-19. Andriuta et al[10] detected antibodies against S1 protein, S2 protein, and nucleoprotein of the SARS-CoV-2 in the CSF of two patients who presented with encephalopathy. Similarly, Benameur et al[11] demonstrated the presence of IgM for SARS-CoV-2 S1 and envelop proteins in three patients with COVID-19 having encephalitis. Interestingly, PCR analysis for viral RNA in the CSF of the patients in both studies yielded negative results. This observation is consistent with CSF findings from other viral encephalities such as the Japanese encephalitis[12] and dengue fever,[13,14] where antibodies against these viruses were isolated in CSF samples in the absence of viral RNA. These preliminary findings suggest that anti-SARS-CoV-2 antibodies in CSF may be better indicators than viral RNA for CNS involvement in patients with COVID-19, and should be subject to further investigations to determine validated assays and their specificity and sensitivities.

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CONFLICT OF INTEREST

The author does not have any conflicts of interest with regard to this publication.

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