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Workup of cerebral involvement in patients with COVID-19 – authors' reply

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We thank Scorza et al. for their comments on our article (Chen et al., 2022) discussing the new S protein mutation of SARS-CoV-2 and its potential effects on immune regulation, associated with the apparent increase in the incidence of severe neurological symptoms in Taiwanese pediatric patients.

Our hospital has been a center for referral of COVID-19 cases since the beginning of the pandemic. Initially during the pandemic, pediatric patients presented with mild symptoms and required only supportive care. Starting in April 2022, at the beginning of the Omicron variant outbreak in Taiwan, critical cases with severe neurological symptoms began to be reported. The same phenomenon was reported in Hong Kong and Japan, which are geographically close to Taiwan, at the beginning of their respective Omicron outbreaks. Furthermore, comparison with the sequence data from GISAID database (http//www.gisaid.org/) revealed a high correlation of the S protein K97E mutation reported in these regions with severe pediatric cases. This observation prompted us to draw the presumptive conclusion that the mutation may play a role in causing severe neurological symptoms.

Due to their critical and unstable condition, all patients reported in our article only underwent brain computed tomography (CT) in the emergency room, with no MRI. Only patient-1's image revealed a relatively decreased attenuation of cerebral white matter, indicative of the early manifestation of cerebral edema, confirmed 2 days later

on follow-up brain CT scan. Conversely, the initial brain CT image of other patients showed no abnormalities, and no further neuroimaging was performed as there was no deterioration of clinical status or uncontrolled seizure episodes after admission.

Additionally, the prominently elevated cell count in patient-2's cerebrospinal fluid (CSF) was caused by a traumatic lumbar puncture procedure. Overall, the results of CSF cultures of all patients were negative for both bacteria and viruses. In addition, results of FilmArray® meningitis/encephalitis panel for detecting possible pathogens in the CSF remained negative. These investigations helped rule out the possibility of bacterial and viral meningoencephalitis. Although the results for inflammatory markers among our patients were inconsistent, elevations in these readings were correlated with disease severity. Patients with higher titers had longer pediatric intensive care unit stays. Patient-1 had the highest level and ultimately passed away due to fulminant meningoencephalitis.

We agree with Dr. Scorza that a comprehensive neurological workup is crucial in defining cerebral involvement in pediatric patients infected with the Omicron variant. It is with this approach that we report our real-world experience for improved understanding of the clinical presentation of infections.

Contributions

Chi-Sheng Chen: Conceptualization, data curation, and writing of the original draft. Chia-Ning Chang: Conceptualization, data curation, and writing of the original draft. Shyi-Jou Chen: Conceptualization. Chih-Fen Hu: Conceptualization, data curation, writing, review, and editing. Hung-Sheng Shang: Conceptualization, Writing–Review, and Editing.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

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Ethical Approval Statement

This study was approved by the Institutional Review Board of Tri-Service General

Hospital (TSGHIRB number: C202005041), and was registered on April 14, 2022.

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