Neuroradiology (2022) 64:2101–2102
https://doi.org/10.1007/s00234-022-03057-x

LETTER TO THE EDITOR

Response to: "Before blaming a COVID vaccine for cytotoxic lesions of the corpus callosum all other differentials must be ruled out"

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Received: 14 September 2022 / Accepted: 16 September 2022 / Published online: 23 September 2022

Abbreviations

CLOCCs	Cytotoxic lesions of the corpus callosum
COVID-19	Coronavirus disease 2019
mRNA	Messenger ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
MRI	Magnetic resonance imaging
CSF	Cerebrospinal fluid
MBD	Marchiafava-Bignami disease
ADEM	Acute disseminated encephalomyelitis

To the Editors,

We greatly appreciate the comments by Dr. Finsterer on our previous article describing patients who showed cytotoxic lesions of the corpus callosum (CLOCCs) after coronavirus disease 2019 (COVID-19) messenger ribonucleic acid (mRNA) vaccination, which provided us an opportunity to describe diagnostic strategies for neurological symptoms and to provide further information on Patient 2 [1, 2].

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Regarding the first criticism on our description that side effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinations are not life-threatening, we would like to clarify that this notion is derived from previous studies which evaluated neurological adverse events among healthcare workers after COVID-19 mRNA vaccination [3, 4]. The most common neurological symptoms were headache, dizziness, decreased appetite, muscle spasm, decreased sleep quality, and brain fogging [3, 4]. Nobody doubts that these symptoms are usually considered mild. However, what we emphasized in our article was the importance of early detection of potentially serious neurological manifestations and require adequate therapy as soon as possible, in concordance with the concern by Dr. Finsterer that systemic immunological and vascular adverse reactions to SARS-CoV-2 vaccinations can be fatal [1].

As for the second criticism on insufficient investigation of Patient 2, we apologize for providing wrong information in the previous manuscript [2], and would like to discuss differential diagnosis based on additional clinical data. Examination of the cerebrospinal fluid (CSF) underwent on day 17 and the result was unremarkable (0.7 cells/μL (monocyte count 0.7 cells/μL, polycyte count 0 cells/μL), normal ≤ 5 cells/μL; protein 25 mg/mL, normal 10–40 mg/mL; immunoglobulin G index 0.49, normal < 0.73; and negative oligoclonal band). Blood coagulation test on the same day revealed that the international normalized ratio was 1.09 (normal 0.85–1.15), activated partial thromboplastin time 30.7 s (normal 24.3–36.0 s), and fibrin degradation products 2.0 μg/mL (normal < 4.0 μg/mL). Magnetic resonance angiography of the brain was also unremarkable on day 17. Thus, focal encephalitis, vasculitis, venous sinus thrombosis, and systemic autoimmune disorders are unlikely. In addition, no abnormality was shown by ophthalmologic observation of anterior ocular segment and of the fundus on day 22. These findings can exclude possibilities of multiple sclerosis, neuromyelitis optica, and other systemic disorders causing retinopathy, vasculitis, and uveitis. MRI of the spinal cord

was not performed because neurological examination did not indicate myelitis; dysesthesia distributed in distal part of all limbs, deep tendon reflexes were normal, abnormal reflexes including Babinski signs were negative, and there was no urinary or bowel dysfunction. Considering the full improvement of splenial lesion in MRI on day 29 [2], and lack of abnormality in perfusion-weighted imaging 2 months later, ischemic stroke and atherosclerosis are quite unlikely. Marchiafava-Bignami disease (MBD) should be considered in patients with chronic alcohol abuse. In its acute form, the genu and splenium of the corpus callosum are commonly involved, and MRI shows T1-weighted hypointensity, T2-weighted and fluid-attenuated inversion recovery image hyperintensity, and often with restricted diffusion within the corpus callosum [5]. In contrast, our Patient 2 was an occasional alcohol drinker, and her blood test showed no sign of hepatic dysfunction or malnutrition. Serum vitamin B_1 was 39 ng/mL (normal 24–66 ng/mL) and vitamin B_{12} was 218 pg/mL (normal 180–914 pg/mL) on day 17. CLOCCs are defined as highly restricted ovoid lesions in the midline of the splenium as shown in our patients [2], whereas lesions of the corpus callosum in patients with MBD widely distribute with blurred margin, and thus are usually not described as CLOCCs. Diagnosis of acute disseminated encephalomyelitis (ADEM) require pleocytosis in the CSF. Lesions of ADEM typically reside in the deep and subcortical white matter and can occur in the thalamus and basal ganglia. We would like to remind that contrast-enhanced MRI is useful to evaluate ADEM but sole involvement of corpus callosum is rare [2]. General physical examination of Patient 2 was not suggestive of influenza and other viral infections; the patient was afebrile and there was no sign of inflammation of the upper respiratory tract. Though, in immunocompromised hosts, it is recommended to investigate possibility of infections and to consider antibacterial, antiviral, and antimycotic prophylaxis before starting immunotherapy.

Admitting that precise diagnostic procedure is crucial and therapeutic intervention should be based on the most plausible diagnosis, full establishment of diagnosis requires at least several weeks, causes delay in treatment, and directly affects prognosis of patients in clinical practice. Correlation between radiological characteristics of lesions involving the corpus callosum including CLOCCs and various neurological disorders will enable us to establish diagnostic and therapeutic strategies from etiological point of view.

Funding This study was partially supported by JPJSBP 120217720.

Data availability The data that support the findings of this study are available on request from the first author [H.O.]. The data are not publicly available due to information that could compromise research participant privacy.

Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethics approval and consent to participate The examinations were performed as a part of an intensive clinical evaluation. On the basis of the noninvasive case-accumulation study design with assured anonymity, the current study was exempt from the need for the institutional ethics committee approval.

Consent for publication Written informed consent was obtained from the patients.

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