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Correspondence

Sudden Death Is More Likely to Result From SARS-COV-2 Infection Than Multiple Sclerosis

Josef Finsterer

Neurology & Neurophysiology Center, Vienna, Austria

▸ See the article "Sudden Death Associated With Possible Flare-Ups of Multiple Sclerosis After COVID-19 Vaccination and Infection: A Case Report and Literature Review" in volume 38, number 10, e78.

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Address for Correspondence:
Josef Finsterer, MD, PhD
Neurology and Neurophysiology Center,
Postfach 20, 1180 Vienna, Austria.
Email: fifigs1@yahoo.de

ORCID iD
Josef Finsterer
https://orcid.org/0000-0003-2839-7305

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To the Editor:

We read with interest the article by Jeon et al.[1] on a 19-year-old man with a history of unilateral optic neuritis, who died suddenly six months after SARS-CoV-2 vaccination with the second dose of the Biontech Pfizer vaccine (BPV). Autopsy revealed multifocal discoloration of the white matter, active and inactive demyelinating plaques around cortical and white matter veins, perivascular lymphocytic infiltration, and microglial proliferation.[1] The sudden death was attributed to laryngospasm or malignant ventricular arrhythmia (MVA) triggered by an end-stage seizure.[1] The study is excellent but has limitations that raise objections that should be discussed.

The main limitation of the study is that the neurological diagnosis remained unclear despite extensive intra vitam work-up and autopsy. The patient was diagnosed with multiple sclerosis postmortem, which is quite unusual especially in light of the pronounced cerebral lesions. In addition, the acute SARS-CoV-2 infection was held responsible for an acute exacerbation of multiple sclerosis and the anti-SARS-CoV-2 vaccination has also been brought into play as a causative factor.

I disagree that the patient died from an exacerbation of multiple sclerosis for several reasons. First, the patient was never diagnosed with multiple sclerosis intra vitam. Second, MRI findings after the first seizure were not interpreted as typical of multiple sclerosis. There is no mention that the patient met the Barkhof criteria.[1] Third, cerebrospinal fluid (CSF) findings after the first seizure were not indicative of multiple sclerosis. Aquaporin-4 antibodies were negative and myelin oligodendrocyte glycoprotein (MOG) antibodies have not been reported. Fourth, cerebral lesions found at autopsy should have already become symptomatic intra vitam with muscle weakness, sensory disturbances, visual impairment, or urinary problems. The autopsy results of the myelon are also not mentioned. Because multiple sclerosis often manifests with myelitis, screening for myelitis would have been crucial to confirm the diagnosis. It may be helpful to revise the records for symptoms of multiple sclerosis and to retake the history with a close relative.

I disagree with the notion that the vaccination with BPV played a causative role. The latency between vaccination and sudden death was six months, ruling out a causal relationship. I also disagree that the second BPV dose three months after vaccination was causal for the onset of epilepsy. Here too, the latency period between vaccination and the first seizure is too long to consider causality. With regard to cortical vein thrombosis, which was diagnosed three months after the vaccination, a causal connection with the vaccination cannot be ruled out with certainty.

I disagree with the statement that the sudden death occurred "under benign circumstances".[1] The patient died during SARS-CoV-2 infection, had a history of optic neuritis, meningoencephalitis, and epilepsy. These were not favourable circumstances.

Differential diagnoses not considered in the index patient include cerebral vasculitis, lymphoma, MOG antibody disorder, acute, and central nervous system (CNS) involvement in COVID-19 (neuro-COVID). Lymphoma could also explain meningeal enhancement.

A limitation of the study is that the patient did not undergo postmortem brain imaging and postmortem CSF assessment. Of particular interest would be the RT-PCR for SARS-CoV-2 and cytokine and chemokines, shown to be upregulated in the CSF in patients with CNS involvement in COVID-19.[2]

No information is given as to whether the cerebral MRI was performed with or without contrast medium. Contrast media use is mandatory to rule out active demyelinating plaques associated with multiple sclerosis.

Since Table 1 of the index article[1] claims to list demyelinating disease relapses after SARS-CoV-2 vaccination in general, demyelinating diseases of the peripheral nervous system, such as Guillain Barre syndrome (GBS), subtype acute, inflammatory, demyelinating polyneuropathy (AIDP),[3] should also be included. Alternatively, only multiple sclerosis patients without neuromyelitis optica cases could be mentioned.

Overall, the interesting study has limitations that put the results and their interpretation into perspective. Clarifying these limitations would strengthen the conclusions and could improve the study. Before diagnosing multiple sclerosis on autopsy, several differential diagnoses need to be ruled out.

Authors' Response to the Letter

We appreciate Dr. Josef Finsterer for his interest and thoughtful comments on our recent publication entitled "Sudden Death Associated With Possible Flare-ups of Multiple Sclerosis After COVID-19 Vaccination and Infection: A Case Report and Literature Review".[1] In this response, we aimed to address the issues raised and provide further clarification on our study.

As Dr. Josef Finsterer pointed out, our case had limitations, especially incomplete clinical work-up including follow-up MRI. We could not access the patient's medical records and did not have a chance to review clinical and laboratory findings, and brain MRIs before the autopsy. His initial presentation was unilateral blurred vision, which was diagnosed as optic neuritis at the ophthalmologic department. At that time, non-contrast enhanced brain MRI showed T2 hyperintense foci involving the periventricular white matter, raising a suspicion of demyelinating disease. But he never visited the neurology department for further evaluation

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of demyelinating disease and was lost to follow-up, until hospitalization for epileptic seizure developed 96 days after COVID-19 mRNA vaccination. During hospitalization, brain MRI revealed T2 hyperintensities in the periventricular region, subcortical white matter, and left basal ganglia. Those lesions mentioned above showed no contrast enhancement while leptomeningeal contrast enhancement in both cerebral convexities were present. Oligoclonal band (OCB) was not detected in the CSF and serum. In the serology test, AQP4-IgG and MOG-IgG were negative as shown in Fig. 1 of the index article.[1] Acute disseminated encephalomyelitis (ADEM) was not included in clinical impression because he did not show clinical manifestation including encephalopathy, such as behavioral changes and alteration in consciousness. Under the clinical impression of meningoencephalitis, he was treated with antiviral/antibiotic medications and anticonvulsant, even though no evidence of bacterial or viral infection in CSF was identified. Unfortunately, the spinal cord was not evaluated by imaging before death and postmortem examination; and postmortem imaging and CSF assessment were not performed.

In our case, diagnosis of multiple sclerosis was established by postmortem findings. At autopsy, demyelinated lesions involved the characteristic periventricular/subependymal regions, optic nerve/chiasm and corpus callosum rather than deep gray matter. Microscopically, most of the periventricular plaques consisted of chronic active or inactive plaques. Acute demyelinating lesion was scarcely seen. MS plaques of the perivenular location were also seen in the small lesions but not predominant. These distribution patterns and different age of plaques favored MS rather than ADEM. As Dr. Josef Finsterer pointed out, CSF findings in our case were not indicative of MS. Our case did not show CSF-specific OCBs that are highly prevalent in MS, but not every patient with MS has CSF-specific OCBs. MS patients in Asian populations are documented to exhibit a relatively lower prevalence of OCBs in CSF analysis in comparison to patients from Western countries.[4-6] The absence of CSF-OCBs in our case might be attributed to ethnic traits.

As Dr. Josef Finsterer commented, differential diagnosis of our case included CNS vasculitis, lymphoma, MOG-AD, CNS involvement of COVID-19 or ADEM. CNS vasculitis or lymphoma was histologically distinguished by absence of transmural inflammatory infiltrate and fibrinoid necrosis, and mixed population of mature B-and T-lymphocytes. MOG-AD can present with aseptic meningitis with leptomeningeal enhancement on imaging and concurrent demyelinating lesions.[7] But anti-MOG IgG was not detected, as shown in Fig. 1 of the index article[1] and the possibility of MOG-AD was less likely considered. Postmortem CSF or brain tissue was not evaluated for SARS-COV-2 in our case, and we could not completely exclude the possibility of direct CNS involvement by SARS-CoV2 infection. According to the clinical and limited pathological data that were previously reported in SARS-CoV-2 infection, hypoxic changes are the most frequently reported alterations of the brain, followed by ischemic and hemorrhagic lesions and reactive astrogliosis and microgliosis.[8] These neuropathological findings may be the results of systemic inflammation and coagulopathy caused by SARS-CoV-2 infection. Viral encephalitis and meningitis are expected to be one of the common neuropathological findings, but they are not verified by neuropathological studies. In our case, the loss of Purkinje cells with Bergmann gliosis was noted in the cerebellum, but it was considered as non-specific hypoxic changes by repeated attack of seizure.

ADEM is the most important differential diagnosis in our case. Acute active plaques centered on venules can be seen in both ADEM and MS.[9] However, our case showed predominantly chronic active or inactive plaques. Although concomitant enhancing and non-enhancing

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of the lesions were not identified in the antemortem brain MRI, the coexistence of acute active, chronic active and inactive plaques in the postmortem microscopic examination suggests the temporal dissemination of the demyelination and it supports the diagnosis of MS. As for the distribution of the lesions, bilateral diffuse lesions with relative periventricular sparing and involvement of deep grey matter/basal ganglia favor ADEM, while lesions in the periventricular/corpus callosal white matter favor MS.[10,11] In our case, demyelinated lesions were multifocal rather than "diffuse", displaying periventricular and corpus callosal involvement. Interestingly, antemortem MRI after the first seizure revealed focal T2 hyperintensity in the left basal ganglia. However, despite pathological examination throughout basal ganglia and thalamus, demyelinated or remyelinated lesion was not identified. According to the consensus-driven criteria based on pediatric cohorts, ADEM is defined as the first clinical event with acute or subacute onset, usually resulting in encephalopathy.[12] However, the deceased had a history of unilateral optic neuritis, which might have been the first manifestation of inflammatory demyelinating disorder. The typical presentation and remission of ON in our case is different from the monophasic inflammatory demyelination process of ADEM.

Our case showed a leptomeningeal enhancement of the bilateral convexity in neuroimaging, which was clinically suspected as meningoencephalitis. At autopsy, meninges were carefully examined but did not show thickening or discoloration. Microscopically, lymphoid infiltrates were observed but it was localized to the meningeal perivascular areas. Meningeal inflammation was frequently reported at autopsy in MS patients[13] and leptomeningeal contrast enhancement occurs frequently in MS and in vivo marker of inflammation and associated subpial demyelination.[14,15] Therefore, it is possible that the meningeal enhancement observed in our case may have been related to meningeal inflammation and subpial demyelination. In our case, brain cortex, adjacent to meningeal inflammation revealed band-like vacuolation, suggesting cortical demyelination. But we could not confirm the cortical demyelination because immunohistochemical markers for myelin were not available in our laboratory.[16,17] Cortical demyelination in MS show little or no inflammation and is poorly discerned with Luxol-fast blue stain.

Vaccines, as well as infections, may occasionally trigger autoimmune responses. Recently, exacerbation of demyelinating disorders of the peripheral nervous system including GBS after COVID-19 vaccination has been reported.[3,18] We summarized previously reported cases of MS that were either discovered or relapsed after SARS-CoV-2 vaccination in Table 1 of the index article,[1] but in the title of Table 1 of the index article[1] we used a broad term "demyelinating disease" to include not only MS but also cases within the category of neuromyelitis optica spectrum disorders.

Since little is known about the exact mechanism of seizure in patients with MS, it seems inappropriate to declare the onset of seizure as the same as the initiation point of the pathologic exacerbation. Also, the deceased had received a second dose of the COVID-19 mRNA vaccine six months prior to the COVID-infection. It would be more reasonable to assume that the deceased's immunological response to COVID-19 infection was somewhat affected by previous vaccinations. However, in our case, the latency period between vaccination and the first seizure is longer than those mentioned in Table 1 of the index article.[1]

In our case, venous sinus thrombosis (VST) was demonstrated in brain MRI 8 days after seizure. Since VST is a common complication following SARS-CoV2 vaccine and seizure is

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a clinical symptom in VST, seizure could be causally related to cerebral venous thrombosis (CVT) in our case. However, the occurrence of VST following COVID-19 vaccination is longer than those described in previously reported cases.[19-21] The fact that seizure persisted until the death and thromboemboli were not found at autopsy suggests that seizure may be related to underlying brain lesions.

The deceased was found dead under his bed, within his sleeping bag, presumably having died during sleep. We used the term "benign circumstances", which refer to situations that are generally less risky or relatively safe compared to those where sudden death would be expected such as trauma, drowning, et cetera, irrelevant of his medical status.[22] Since no other external causes of death were found, we think that the term "benign circumstances" seems appropriate.

In conclusion, we appreciate Dr. Josef Finsterer's valuable feedback and generally agree with the comments and acknowledge the limitations of our study. We hope that our response provided additional clarification of our report.

Yo han Jeon[1], Sangjoon Choi[1], Ji Hyun Park[1], Jong Kyu Lee[1], Nam Seok Yeo[1], SangHan Lee[1], and Yeon-Lim Suh[2]

[1]Department of Forensic Medicine, Defense Institute of Forensic Science, Criminal Investigation Command, Ministry of National Defense, Seoul, Korea

[2]Department of Pathology and Translational Genomics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Address for Correspondence

SangHan Lee, MD, PhD

Department of Forensic Medicine, Defense Institute of Forensic Science, Criminal Investigation Command, Ministry of National Defense, 22 Itaewon-ro, Yongsan-gu, Seoul 04383, Korea. sanghan111@gmail.com

Yeon-Lim Suh, MD, PhD.

Department of Pathology and Translational Genomics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea. ylsuh76@skku.edu

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