Symmetric DWI hyperintensities in CMT1X patients after SARS-CoV-2 vaccination should not be classified as stroke-like lesions

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Letter to the Editor

We read with interest the article by Zhang et al. on a 39 years-old male with two episodes of asyndesis, dysphagia, and dyspnea 27 days after the second dose of a non-specified, Chinese anti-SARS-CoV-2 vaccine [1]. The individual history was positive for chronic eczema and kidney stones. The family history was positive for pes cavus in two brothers, and Charcot-Marie-Tooth (CMT) disease in one of them [1]. Neurological exam revealed chewing weakness, bulbar weakness, reduced tendon reflexes, discrete muscle wasting, and pes cavus [1]. Genetic work-up revealed the variant c.65G>A in *GJB1* which is why CMT1X was diagnosed [1]. Despite documentation of the genetic defect, CMT1X was interpreted as side effect of the anti-SARS-CoV-2 vaccination [1]. The study is excellent but raises concerns.

We disagree with the notion that "CMT1X can occur after SARS-CoV-2 vaccination" suggesting that the vaccination caused CMT1X, that SARS-CoV-2 vaccination is a predisposing factor for CMT1X, and that there are predisposing factors for CMT1X, such as fever, high-altitude travel, or excessive physical activity [1]. CMT1X is a genetic disorder and not an infectious or immunological disease. There is no causal relation between SARS-CoV-2 and CMT1X. However, infectious or immunological disease may occasionally modify the phenotype of CMT1X.

We disagree with the use of the term "stroke-like episode" (SLE) [1]. SLE is a phenomenon predominantly occurring in primary mitochondrial disorders (MIDs), particularly in mitochondrial encephalopathy, lactic acidosis, and stroke-like episode (MELAS) syndrome, for which SLEs are pathognomonic [2]. SLEs are the clinical correlate of a stroke-like lesion (SLL), which are transient, dynamic cerebral lesion, most commonly originating from the cortex, and not consistent with a vascular territory and have a characteristic pattern on imaging.

We disagree that the diffusion-weighted imaging (DWI) lesions shown in figure 2 represent SLLs [1]. SLL's have typically a dynamic course with initial expansion of the lesion and regression after a nadir has been reached. SLL's end up as white matter lesion, focal atrophy, cyst formation, laminar cortical necrosis, or toenail sign [3]. Occasionally, SLLs disappear without a residual lesion. SLLs can be identified and delineated from differential abnormalities by multimodal magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), magnetic resonance angiography (MRA) and fluor-deoxy glucose-positron emission tomography (FDG-PET). On multimodal MRI, SLLs typically present as hyperintensity on T2, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI),

and perfusion-weighted imaging (PWI) [4]. SLLs are hypointense on T1 and oxygen-extraction fraction (OEF)-MRI. MRS of SLLs typically shows a reduced N-acetyl aspartate (NAA) peak and a lactate peak. MRA commonly shows dilation of arteries supplying the area of the SLL [4]. On FDG-PET, a SLL typically manifests with hypometabolism. Another argument against a SLL pretended to be shown in figure 2 is that the lesions were symmetric. SLLs are almost always symmetrical. Another argument against a SLLs is that these lesions did not show the typical dynamics of a SLL. SLL usually expand until a nadir before they regress again and either completely disappear or remain to a lesional stage [4]. Another argument against SLLs is that they usually are associated with seizures or epileptiform discharges on EEG but the patient's individual history was negative for seizures. Lesions shown in figure 2 do not meet these criteria. Therefore, they cannot be classified as SLLs and thus the clinical correlate cannot be a SLE.

A limitation of the study is that no electroencephalogram (EEG) was recorded. SLLs are commonly associated with seizures or even triggered by seizures [5]. Furthermore, the episodic nature of the clinical manifestations aphasia and dysphagia suggest seizure activity. In addition, the transient DWI hyperintensities could be also triggered by seizures. Therefore, it is mandatory to search the history for seizures and to record an EEG.

An argument against a causal relation between SARS-CoV-2 vaccination and the cerebral lesions is the long latency of 37 days between vaccination and the MRI. Several other causes should have been ruled out. An argument for a causal relation is that DWI hyperintensities of the corpus callosum have been previously reported as side effects of SARS-CoV-2 vaccinations [6].

Because the index patient was diagnosed with a genetic disorder, it is mandatory to investigate all clinically affected and unaffected first-degree relatives for the causative variant. Family screening for the culprit variant is essential for assessing the progression and outcome of the disease and for genetic counselling.

It is not comprehensible why the previous history was not positive for pes cavus. Because pes cavus was described on the clinical neurologic exam, the patient should have noticed it already by himself. We should also know whether the patient recognised any phenotypic manifestations of hereditary neuropathy? Did he complain about paresthesias, dysesthesias, allodynia, numbness, or pain insensitivity? Surprisingly, clinical exam did not reveal aphasia [1]. We should know why?

It is not comprehensible why the index patient received steroids and intravenous immunoglobulins simultaneously. A possible therapeutic effect cannot be attributed to either of the two if they are given in common.
Because the cerebral lesions do not explain the bulbar symptoms, CMT1X should be considered as causative.
Overall, the interesting study has limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Symmetric DWI hyperintensities in CMT1X patients after SARS-CoV-2 vaccination should not be classified as SLLs.

Declarations

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