eNeurologicalSci 34 (2024) 100492

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci

FLAIR hyperintense cortical lesions in anti-myelin oligodendrocyte glycoprotein antibody-associated encephalitis with seizure following SARS-CoV-2 mRNA vaccination

ARTICLE INFO

Keywords
Anti-myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)
FLAIR-hyperintense lesions in anti-MOG-associated encephalitis with seizures (FLAMES)
Severe acute respiratory syndrome coronavirus 2
Vaccination

Dear Editor

Myelin oligodendrocyte glycoprotein (MOG) is a major oligodendrocyte protein localized on the superficial outer layer of the myelin sheath and, therefore, can likely be an immunological target leading to demyelination once autoantibodies are formed. Recent research has identified anti-MOG antibody-associated disease (MOGAD), which can cause neuromyelitis optica spectrum disorder, optic neuritis, myelitis, encephalitis, and acute disseminated encephalomyelitis [1,2]. Furthermore, fluid-attenuated inversion recovery (FLAIR) hyperintense cortical lesions in anti-MOG antibody-associated encephalitis with seizure (FLAMES) has been proposed as another MOGAD phenotype characterized by seizures, headache, fever, and abnormal FLAIR images linked to neurological abnormalities [3,4]. MOGAD [5], including FLAMES [6], can develop in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, *i.e.,* COVID-19. Moreover, there are increasing reports of MOGAD following SARS-CoV-2 mRNA vaccination, although the detailed mechanisms and causal relationships remain unknown [7]. Here, we report a case of a middle-aged man who developed FLAMES following SARS-CoV-2 mRNA vaccination.

1. Case description

A 42-year-old healthy man had a generalized tonic-clonic seizure (GTCS) 14 days after receiving the second dose of the BNT162b2 mRNA vaccine (Pfizer/BioNTech), following the first dose of the same vaccine three weeks previously. He was admitted to our hospital due to another GTCS five days later. Both seizures ceased spontaneously within a few minutes and were accompanied by headache and disorientation. He had normal visual acuity and visual field, without meningeal irritation, motor and sensory deficits, abnormal or pathological reflexes, or bladder and bowel dysfunction.

Complete blood cell counts and blood chemistry were normal, except for an elevated creatine kinase level (3128 U/L). Serum samples were positive for anti-thyroglobulin and anti-thyroid peroxidase antibodies, with normal levels of thyroid-stimulating hormone and free T4. Autoantibodies against the amino-terminus of alpha-enolase, anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti-glutamic acid decarboxylase antibodies, and rheumatoid factor were negative, whereas anti-MOG antibody assessed by a live cell-based assay [8] was positive in the serum. Cerebrospinal fluid (CSF) showed mild monocytic pleocytosis (30 /μL), elevated total protein (65 mg/dL), and elevated interleukin-6 (69.1 pg/mL) without anti-MOG antibodies and oligoclonal IgG. PCR tests for herpes simplex and varicella-zoster virus, Gram staining, and CSF culture were all negative. Interferon-gamma release assay for *Mycobacterium tuberculosis* and β-D-glucan were negative in the blood. Electroencephalography revealed a disorganized posterior-dominant rhythm and sharp transients in the left frontal region without epileptic discharges during the interictal state. Brain magnetic resonance imaging (MRI) on admission showed FLAIR hyperintensity with gadolinium enhancement in the parasagittal cortex of the bilateral frontal and parietal lobes, whereas hyperintensity was not evident on DWI, T2WI, or gadolinium-enhanced T1WI (Fig. 1A, B, C, D).

We diagnosed the patient with anti-MOG antibody-associated FLAMES and initiated intravenous methylprednisolone ([IVMP]; 1000 mg/day for three days), followed by oral prednisolone (PSL) starting at 60 mg/day. Steroid therapy improved the patient's disorientation without seizure relapse. Brain MRI on day 22 revealed that the cortical FLAIR hyperintensity with gadolinium enhancement disappeared (Fig. 1E, F). Lumbar puncture revealed decreased cell count and protein levels in the CSF. Although treatment with PSL was effective, we discontinued because of the development of delirium on day 30. However,

Abbreviations: CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; FLAMES, FLAIR hyperintense cortical lesions in anti-MOG antibody-associated encephalitis with seizure; GTCS, generalized tonic-clonic seizure; IVMP, intravenous methylprednisolone; MOG, myelin oligodendrocyte glycoprotein; MOGAD, anti-MOG antibody-associated disease; MRI, magnetic resonance imaging; PSL, prednisolone.

https://doi.org/10.1016/j.ensci.2023.100492
Received 10 October 2023; Accepted 19 December 2023
Available online 22 December 2023

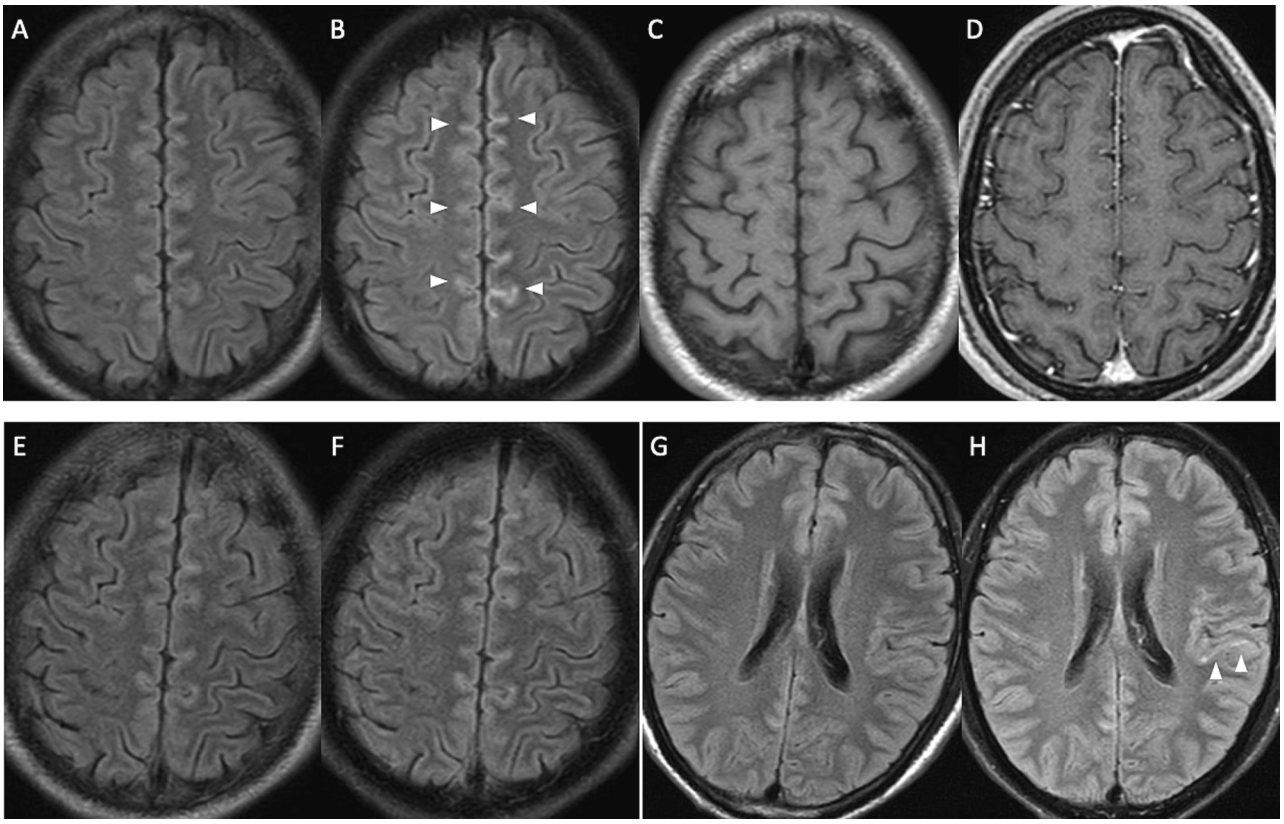

Fig. 1. (A), (B), (C), and (D), magnetic resonance imaging (MRI) on admission. Fluid-attenuated inversion recovery (FLAIR) imaging (A) shows cortical swelling with gadolinium enhancement (B) in the parasagittal cortex of bilateral frontal and parietal lobes. Hyperintensity was not evident in plain (C) and gadolinium-enhanced (D) T1 weighted images. (E) and (F), MRI on day 22 after admission, following the first intravenous methylprednisolone. FLAIR imaging (E) showed the attenuation of the cortical swelling. Gadolinium enhancement also disappeared (F). (G) and (H), MRI on day 48 after admission, performed one week after oral prednisolone discontinuation. FLAIR imaging (G) revealed the relapse of cortical swelling of the left temporal lobe with gadolinium enhancement (H).

because the brain MRI revealed asymptomatic cortical FLAIR hyperintensity with gadolinium enhancement in the left lateral temporal lobe one week after PSL discontinuation (Fig. 1G, H), we retreated the patient with a lower dose of IVMP (500 mg/day) intravenously for three days, followed by oral PSL (10 mg/day). The cortical FLAIR hyperintensities disappeared after steroid therapy. The patient was discharged home nine weeks after admission and had no recurrence for at least 20 months with slow tapering of PSL.

2. Discussion

We diagnosed the patient with FLAMES based on the following findings: 1) seizure and headache; 2) FLAIR images characteristic of FLAMES; 3) the presence of serum anti-MOG antibody; and 4) a favorable response to steroid therapy [3,4].

Since the patient received a second dose of the SARS-CoV-2 mRNA vaccine two weeks before the development of FLAMES, with an interval of three weeks from the first vaccination, we considered that the mRNA vaccine producing the spike protein caused FLAMES. FLAMES have been reported to develop during COVID-19 [6], suggesting that the components of SARS-CoV-2, including the spike protein, alone, can cause FLAMES. The mechanism by which the SARS-CoV-2 mRNA vaccine induces the production of anti-MOG autoantibodies in previously healthy patients is unknown. The vaccine may non-specifically activate occult anti-MOG antibodies, as reported in a 45-year-old woman with relapsing MOGAD following mRNA booster vaccination [9]. The simultaneous manifestation of thyroid autoantibodies in this patient supports the concept of nonspecific vaccine-mediated autoantibody activation. Repeated vaccinations within a short interval may boost immunological responses, leading to enhanced production of autoantibodies in this case [7,9]. However, we cannot exclude the possibility that the vaccine specifically induces the production of anti-MOG antibodies, causing FLAMES.

Why did the vaccine induce FLAMES among the MOGAD phenotypes? The SARS-CoV-2 spike protein can bind to angiotensin-converting enzyme 2, highly expressed in small vascular cells, such as endothelial cells and pericytes, and can damage small cerebral vessels forming the blood brain barrier (BBB) [10]. Because the BBB in the gray matter is more vulnerable than that in the white matter [11], an anti-MOG autoantibody may pass through damaged small vessels and cause perivascular demyelination and inflammation, a pathological characteristic of FLAMES, preferentially in the gray matter in SARS-CoV-2 mRNA vaccine-related MOGAD [12,13]. Although a previous report suggested that the spinal cord and brainstem may often be involved in vaccine-mediated MOGAD [7], we should note that FLAMES may be underdiagnosed because of its mild neurological symptoms and radiological findings. The fact that anti-MOG antibody was positive only in the serum, but not in the CSF, may also be interesting in the present case because a recent study reported CSF positivity in MOGAD cases presenting with cortical encephalitis [8].

In the present case, FLAMES relapsed during PSL discontinuation; however, re-administration of steroid therapy immediately remitted the disease state. These clinical courses suggest that steroid therapy is effective for MOGAD/FLAMES [7,14]. Moreover, they support the concept that steroid therapy should be slowly and carefully tapered in patients with SARS-CoV-2 vaccine-associated MOGAD [7].

Funding

This research did not receive any specific grant from funding

agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Fumitaka Yoshino: Conceptualization, Project administration, Writing – original draft, Writing – review & editing. **Yuichi Ozaki:** Writing – review & editing. **Tomoya Shibahara:** Writing – review & editing. **Mikiaki Matsuoka:** Writing – review & editing. **Masaki Tachibana:** Writing – review & editing. **Tetsuro Ago:** Supervision, Writing – review & editing. **Takanari Kitazono:** Writing – review & editing. **Junya Kuroda:** Supervision, Writing – review & editing. **Hiroshi Nakane:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank the patient for giving consent for publishing the details of the case. We also thank Editage (www.editage.com) for English language editing.

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