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Atypical Myelin Oligodendrocyte Glycoprotein Immunoglobulin G-Associated Disorder With Recurrent Meningoencephalitis

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Dear Editor,

The most common features of myelin oligodendrocyte glycoprotein immunoglobulin G (IgG)-associated disorder (MOGAD) are optic neuritis in adults and acute disseminated encephalomyelitis (ADEM)-like features in children.[1] Meningeal involvement in MOGAD is uncommon. Here we report an uncommon case of MOGAD in a patient who showed recurrent meningoencephalitis but no typical MOGAD features. The patient responded well to active immunosuppressant therapy.

A 22-year-old male visited a local hospital with high fever and headache that first appeared 2 days previously. He had no neurological deficits other than neck stiffness. Initial brain MRI revealed high signal intensities in both medial thalami (Fig. 1A) and the cerebral cortex (Fig. 1B) on fluid-attenuated inversion recovery (FLAIR) sequences, and diffuse leptomeningeal enhancement on contrast-enhanced T1-weighted images (Fig. 1C and D). Cerebrospinal fluid (CSF) analysis showed a cell count of 370/μL (neutrophils, 45%; lymphocytes, 54%), an elevated protein level (108.8 mg/dL), and normal glucose levels (CSF glucose, 50 mg/dL; serum glucose, 90 mg/dL). The CSF cultures for bacteria, acid-fast bacillus, and fungus, and India ink staining for cryptococcus were all negative. The CSF viral polymerase chain reactions of HSV1, HSV2, CMV, VZV, EBV, Japanese encephalitis virus, JC virus, HHV6, and HHV8 were also negative. Empirically, he was administered ceftriaxone (1 g/day for 2 weeks), doxycycline (100 mg twice daily for 2 weeks), and acyclovir (10 mg/kg three times a day for 2 weeks) based on a diagnosis of infectious meningoencephalitis of unknown cause. CSF follow-up tests performed 1 week later revealed improvement, with a cell count of 15/μL (lymphocytes, 88%; monocytes, 12%), but his mental status had worsened to stupor. At that time we checked anti-Hu, anti-Yo, anti-Ri, anti-NMDA-R, anti-LGI1, anti-CASPR2, and anti-AMPA-R antibodies (Abs) based on suspicion of autoimmune encephalitis, but all findings were negative. Suspecting autoimmune meningoencephalomyelitis of unknown cause, we treated the patient with methylprednisolone (1,000 mg/day for 5 days) and intravenous immunoglobulin (IVIg) (400 mg/kg/day for 5 days) simultaneously following 2 weeks of antibiotics treatment. Since he did not respond to either drug, rituximab (375 mg/m^2 once a week for 4 weeks) was started the day after both treatments were completed. After the third injection of rituximab treatment, his mental status gradually improved, finally allowing him to speak and move on his own. One month later, he was discharged from the hospital without any neurological deficits [modified Rankin Scale (mRS) score=1] except for subjective memory impairment, and he was continued on 30 mg of oral prednisolone daily. The oral prednisolone dose was reduced to 10 mg in the outpatient clinic. After 3 months of tapering oral steroids, he again started to complain of headache and fever. Increasing the steroid dose improved his symptoms, while reducing the steroid dose resulted in the recurrence of headache and fever. We

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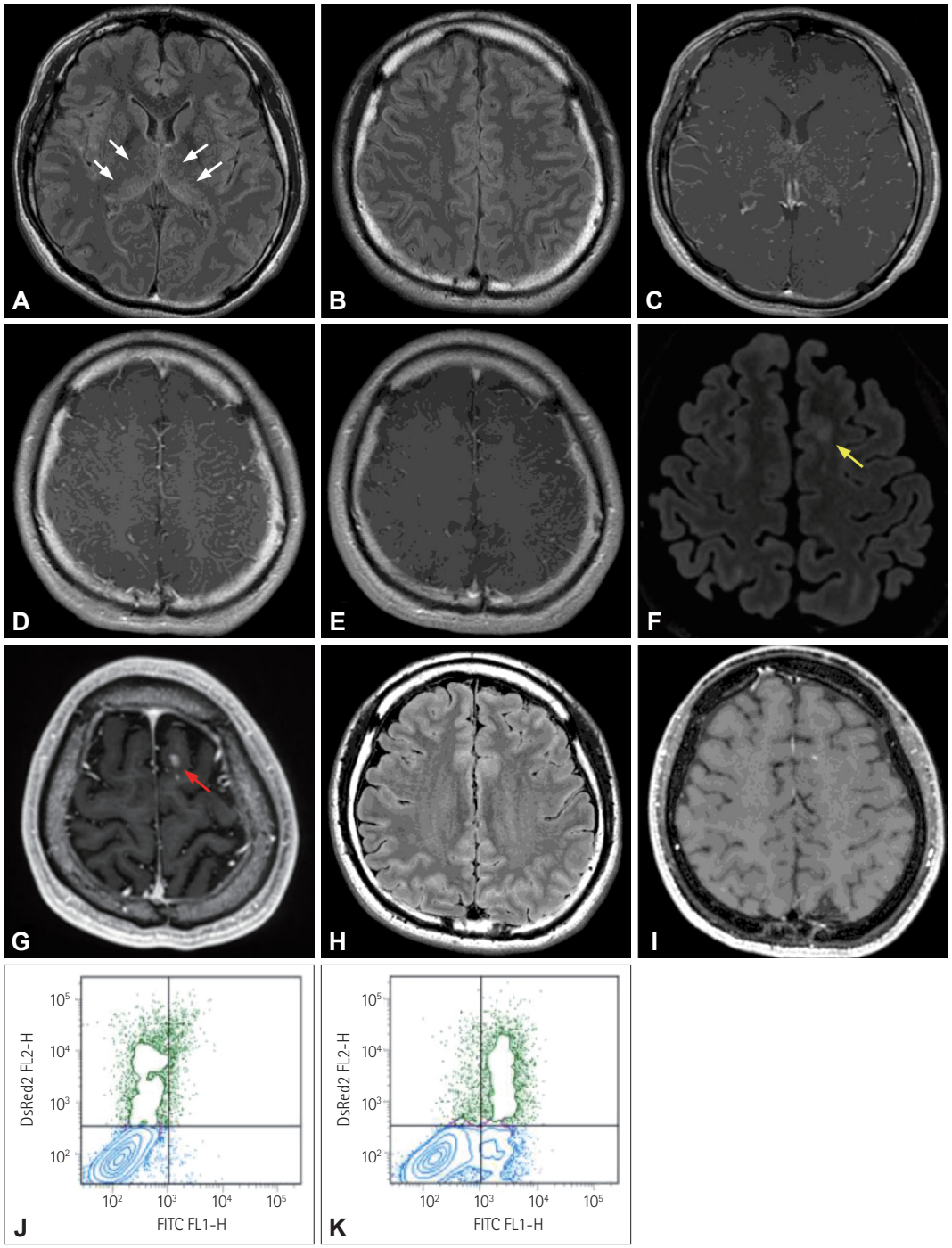

Fig. 1. Initial brain MRI revealed high signal intensities in both medial thalami (A) and the overall sulcus (B) on FLAIR sequences (white arrows), and meningeal enhancement on T1-weighted images (C and D). Brain MRI performed following the appearance of meningeal irritation signs at the second attack revealed meningeal enhancement on T1-weighted images (E) and two focal high-signal-intensity lesions with enhancement in the left medial frontal lobe on FLAIR (F) (yellow arrow) and T1-weighted (G) images (red arrow). After steroid treatment, the extents of the high-signal-intensity lesion in the cerebral sulcus on FLAIR images (H) and the meningeal enhancement on T1-weighted images (I) were decreased. The results of the flow cytometric assay for anti-MOG Ab in a healthy control (J) and the patient (K) displayed as scatter plots with FITC FL1-H on the x-axis and DsRed2 FL2-H on the y-axis. Human embryonic kidney 293T cells were transfected with the pIRES2-DsRed2 vector containing full-length human MOG cDNA, and we used mouse anti-human IgG1 Hinge-FITC. In the healthy control, the scatter plot was primarily concentrated in the upper-left quadrant, because he did not have MOG Abs that bind to antihuman IgG1 Hinge-FITC (J). However, the scatter plot of our patient was primarily concentrated in the upper-right quadrant due to the presence of MOG Abs, which bind to antihuman IgG1 Hinge-FITC, resulting in a right-shifted scatter plot (K). Abs, antibodies; FITC, fluorescein isothiocyanate; FLAIR, fluid-attenuated inversion recovery; MOG, myelin oligodendrocyte glycoprotein.

repeat the CSF analysis, which revealed a cell count of 470/μL (neutrophils, 68%) and that the protein level was also elevated (76.1 mg/dL). There were no positive CSF results for the infectious organisms that had been tested at the first attack. Brain MRI showed meningeal enhancement on contrast-enhanced T1-weighted images (Fig. 1E) and two focal high-signal-intensity lesions with enhancement in the left medial frontal lobe on FLAIR (Fig. 1F) and T1-weighted (Fig. 1G) images. We assumed that the etiology of his disease was immune-mediated rather than infectious, and so we did not prescribe antibiotics or antiviral agents after the second attack. Steroid dose elevation (up to 60 mg) and IVIg retreatment (400 mg/kg/day for 5 days) led to his symptoms improving and normalization of the results obtained in another CSF study. The extents of the high-signal-intensity lesion in the cerebral sulcus on FLAIR images (Fig. 1H) and the meningeal enhancement on the T1-weighted image (Fig. 1I) on brain MRI were decreased. He recovered without any neurological deficits (mRS score=0). At that time we checked anti-aquaporin-4 (AQP4) Ab and MOG-IgG in his serum sample based on suspicion of recurrent CNS demyelinating disease. An in-house cell-based assay was positive for MOG-IgG (Fig. 1J and K) and negative for AQP4-IgG; this in-house cell-based assay has previous been demonstrated to have a specificity of 100% for MOG-IgG.[2] Finally, we diagnosed our patient as MOGAD with recurrent meningoencephalitis. Considering that the typical clinical manifestation of MOGAD is optic neuritis, we evaluated his visual acuity and relative afferent pupillary defect, and performed a Humphrey visual field test; all of the results were within the normal ranges. We continued treating him with IVIg (1 g/kg for 1 day) monthly, which showed a good treatment effect at the second attack, and at the last follow-up he was doing well without relapse.

We have reported here the first case of MOGAD with recurrent meningoencephalitis, in which the patient did not exhibit typical MOGAD features over a 1-year follow-up period. There have been four case reports of MOGAD involving the meninges,[3-6] three of which were adult cases and the fourth was a pediatric case. All of the adult cases were monophasic and accompanied by optic neuritis. The pediatric case was also monophasic, but the patient showed ADEM-like features. In contrast, the present patient experienced two attacks of meningoencephalitis without optic neuritis, and his brain MRI lesions were not compatible with typical ADEM. This case shows that MOGAD should also be considered in patients with recurrent meningoencephalitis even when no typical features are present. Another interesting aspect of our case was the evident involvement of meninges in MOGAD. Nagabushana et al.[4] hypothesized that leptomeningeal involvement was an indicator of blood–brain barrier disruption by preceding infection and permitted access of MOG Abs to the CNS. However, Suzuki et al.[6] reported a patient with MOGAD whose meningeal symptoms persisted for more than 1 month without other neurological deficits, and suggested that aseptic meningitis can be associated with MOG Abs itself, rather than representing a preceding infection. The repeated occurrence of meningitis in the present case also supports that meningeal involvement can be caused by MOGAD itself, rather than by a prodromal infection. Finally, our patient responded well to rituximab. We cannot exclude a delayed effect of methylprednisolone or IVIg, but we have demonstrated that rituximab could be a suitable treatment choice for MOGAD.

Ethics Statement

Written informed consent was obtained from the patient. This study was approved by the local Institutional Review Board.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

Sung-Min Kim, a contributing editor of the *Journal of Clinical Neurology*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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