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【 CASE REPORT 】

Myelin Oligodendrocyte Glycoprotein-antibody-associated Disorder Presenting with Corticomeningeal Encephalitis Prior to the Onset of Optic Neuritis

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Abstract:

We herein report a case of myelin oligodendrocyte glycoprotein-antibody-associated disorder (MOG-AD) presenting with corticomeningeal encephalitis. The patient exhibited oral ulceration, a mild impairment of consciousness, fever, nausea, nuchal rigidity, positivity for human leukocyte antigen type B51, and neutrophil-dominant pleocytosis and interleukin-6 level in cerebrospinal fluid (CSF). Magnetic resonance imaging (MRI) revealed a right temporal lesion with leptomeningeal gadolinium enhancement. The initial diagnosis was neuro-Behçet's disease presenting with meningoencephalitis; however, a cell-based assay detected anti-MOG antibody in the serum and CSF and the patient also experienced bilateral optic neuritis. After administering steroid therapy, his neurologic symptoms and CSF abnormalities improved along with the disappearance of gadolinium enhancement and the lesion on MRI. This case suggests that MOG-AD may present with corticomeningeal encephalitis prior to the onset of optic neuritis.

Key words: MOG-AD, corticomeningeal encephalitis, neuro-Behçet's disease, meningitis, Graves' disease

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Introduction

Myelin oligodendrocyte glycoprotein (MOG)-antibody-associated disorders (MOG-AD) are classified as inflammatory demyelinating disorders of the central nervous system (CNS). Initially, anti-MOG antibody was detected in patients with neuromyelitis optica spectrum disorders, optic neuritis, and transverse myelitis (1, 2). In recent years, some cortical encephalitis cases related with MOG-AD have been reported (3). On the other hand, neuro-Behçet's disease occurs in less than 10 percent of patients with Behçet's disease. Neuro-Behçet's disease can be categorized into parenchymal and non-parenchymal subtypes. The parenchymal type presents with brainstem lesions, cerebral lesions, spinal lesions, and rarely aseptic meningitis and meningoencephalitis (4, 5). Distinguishing MOG-AD from other inflammatory diseases of the CNS is a key imperative to guide treatment decision-making, because MOG-AD shows a good response to steroid therapy. We herein report a patient with MOG-AD who presented with corticomeningeal encephalitis prior to the onset of optic neuritis and who initially was suspected to mimic neuro-Behçet's disease.

Case Report

A 37-year-old Japanese man presented with right orbital headache. His family history was unremarkable. The headache deteriorated despite taking over-the-counter analgesics. One week after the onset, the patient was admitted to a local hospital with a high fever (38.0℃), non-localized headache, nausea, and painless oral ulcers. Neurological examinations revealed nuchal rigidity, jolt accentuation, and Kernig's sign. A cerebrospinal fluid (CSF) examination showed increased the cell count (164 cells/μL; 34% monocytes), total protein level (83.3 mg/dL), and a slightly decreased sugar level (45 mg/dL, blood sugar 102 mg/dL). The patient was treated with intravenous broad-spectrum antibiotics and antivirals for suspected acute infectious meningitis; however, he showed a gradual decrease in his consciousness level. Fig. 1

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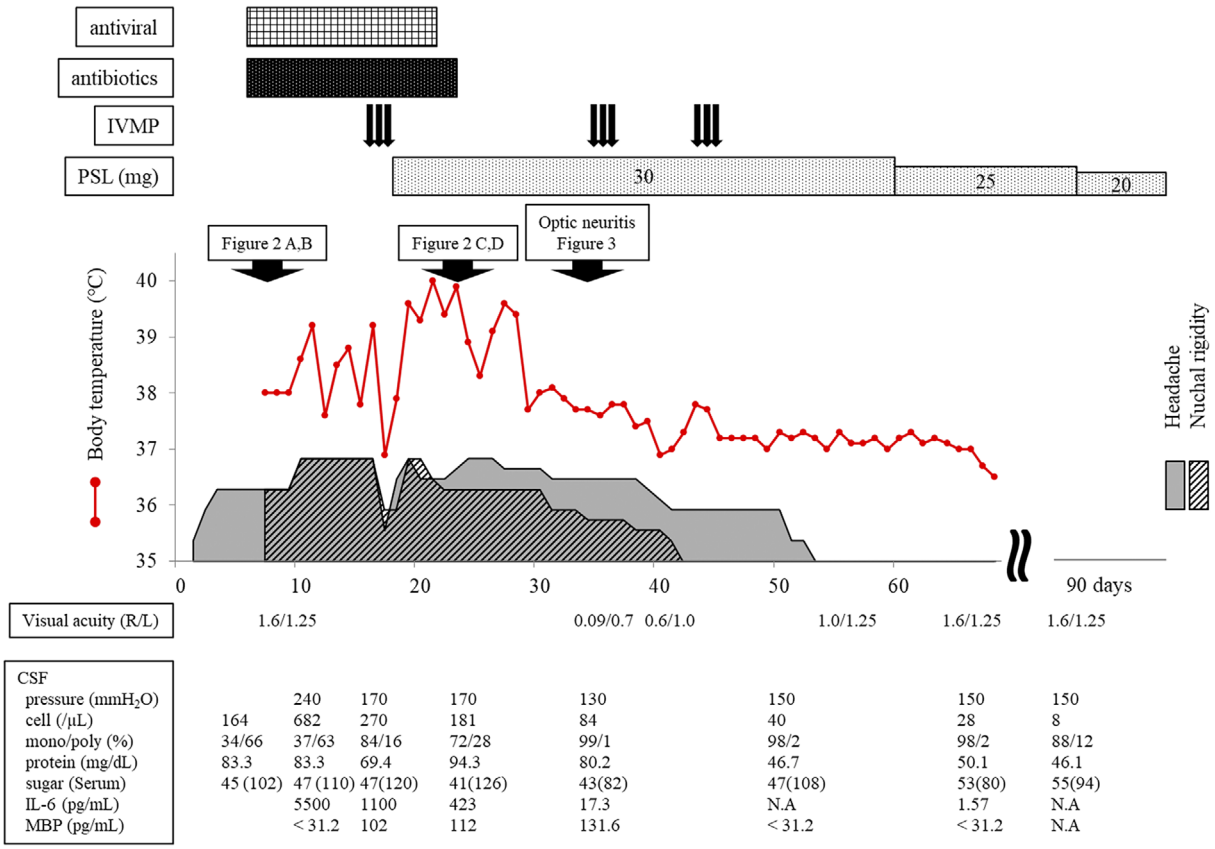

Figure 1. The figure shows the clinical course of the patient. The treatments are described in the upper line, the changes in symptoms are described in the middle line, and laboratory data are described in lower line. IVMP: intravenous pulsed methylprednisolone, PSL: prednisolone, CSF: cerebrospinal fluid, MBP: myeline basic protein, N.A: not available

shows his clinical course. Ten days after onset, he was referred to our hospital for further evaluation. Neurological examinations showed a mild impairment of consciousness and nuchal rigidity, jolt accentuation, and Kernig's sign. His visual acuity was normal (right/left: 1.6/1.25). Routine blood investigations showed leukocytosis (10,670 cells/μL) and a slightly elevated C-reactive protein level (0.36 mg/dL). He was suspected to have aseptic meningitis including autonomic diseases, and thus additional examinations were performed. He tested positive for human leukocyte antigen (HLA) type B51. The serum levels of thyroid-stimulating hormone, free triiodothyronine (T3), and free thyroxine (T4) were <0.005 μIU/mL (normal: 0.50-5.00 μIU/mL), 7.44 pg/mL (normal: 2.3-4.0 pg/mL), and 3.81 ng/dL (normal: 0.90-1.70 ng/dL), respectively. He exhibited positivity for thyrotropin receptor antibody (25.9 IU/L). In addition, serum anti-aquaporin 4-IgG detected by cell-based assay was negative. A CSF examination showed an increased opening pressure (240 mmH_2O), increased cell count (682 cells/μL; 37% monocytes, 63% polymorphonuclear cells), total protein (113.9 mg/dL), and interleukin (IL)-6 level (5,500 pg/mL; normal <4.3 pg/mL). The sugar level in CSF had slightly decreased (47 mg/dL, blood sugar 110 mg/dL), while the IgG index had slightly increased (0.69). Oligoclonal bands were not detected in the CSF. Bacterial and fungal cultures were negative and the antibody indices to Herpes Simplex Virus, Varicella-Zoster Virus, Cytomegalovirus, Epstein-Barr Virus were not elevated. Fluid attenuated inversion recovery image (FLAIR) sequence of brain magnetic resonance imaging (MRI) revealed hyperintense cortical lesions with mild edema in the right temporal lobe (Fig. 2A). Gadolinium-enhanced T1-weighted image showed leptomeningeal enhancement in the right temporal lesions (Fig. 2B). Electroencephalography showed intermittent slow waves in the left frontal region and no epileptiform discharge. The initial laboratory findings were suggestive of neuro-Behçet's disease. However, a cell-based assay detected anti-MOG antibody in the serum (titer 1:2,048; normal <1:128) and CSF (titer 1:64; normal <1:4). Finally, a diagnosis of MOG-AD presenting with corticomeningeal encephalitis and Graves' disease was established. He was administered two courses of intravenous pulsed steroid therapy (methylprednisolone 1,000 mg/day for 3 days) followed by continuation therapy with oral steroids (prednisolone 30 mg/day); his symptoms showed a gradual improvement. Follow-up MRI at 26 days after onset showed disappearance of hyperintense lesions with leptomeningeal gadolinium enhancement on a FLAIR image (Fig. 2C, D). However, he experienced a recurrence of symptoms including bilateral visual impairment (visual acuity 0.09/0.7) at 36 days after onset; repeat MRI showed

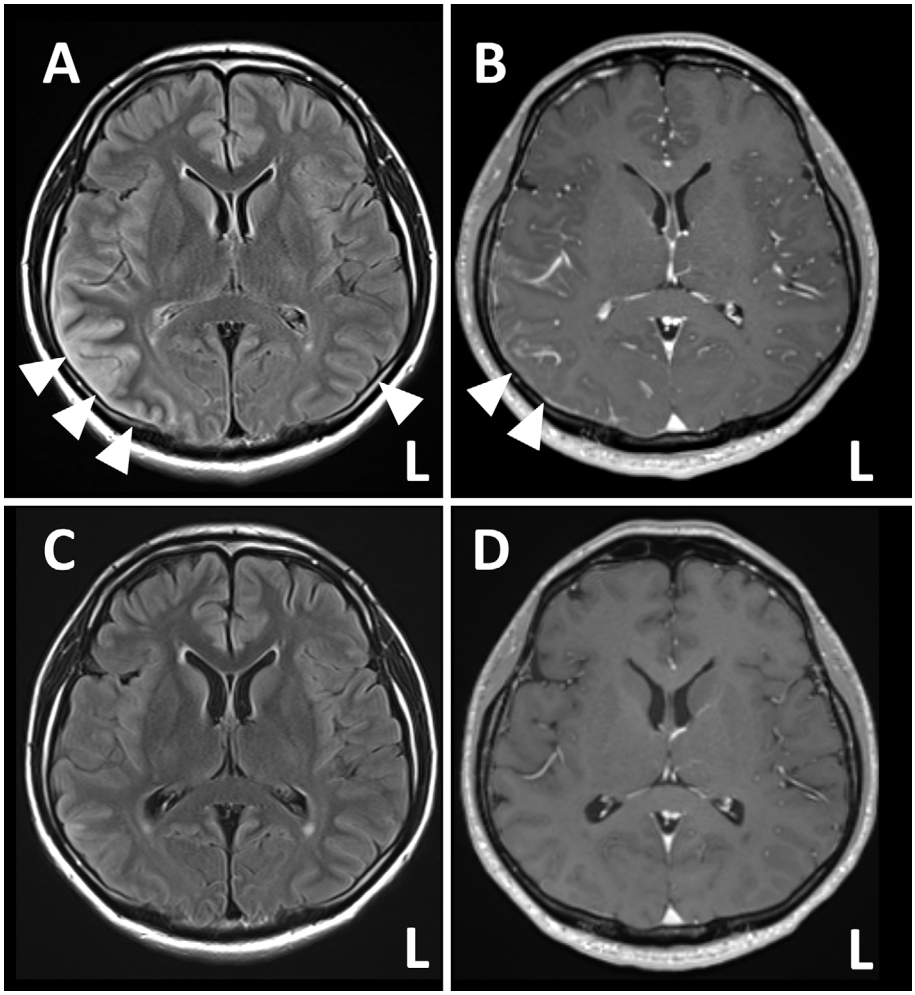

Figure 2. **Magnetic resonance images of the patient on admission (A, B) and on 26th day after onset (C, D). (A) Axial fluid attenuated inversion recovery image (FLAIR) showing hyperintensity and swelling in right-dominant superficial cortex . (B) Gadolinium-enhanced T1-weighted image showing leptomeningeal enhancement in the areas corresponding to hyperintensity in FLAIR. (C) Images on the 26th day after onset showing an improvement of the hyperintensity and swelling (C), and the disappearance of leptomeningeal gadolinium enhancement (D).**

hyperintensity in both optic nerves with mild edema on T2-weighted sequence (Fig. 3A, C) and gadolinium enhancement on gadolinium-enhanced T 1-weighted images (Fig. 3B, D). He was administered an additional two courses of intravenous pulsed steroid therapy and his visual acuity thereafter fully recovered (visual acuity 1.6/1.25). He was discharged while continuing oral steroids (prednisolone 30 mg/day); the clinical course was uneventful after the tapering of steroid therapy.

Discussion

We herein described a patient with MOG-AD who developed corticomeningeal encephalitis followed by bilateral optic neuritis. We diagnosed him to have meningitis because he had fever, nuchal rigidity, nausea, jolt accentuation, Kernig's sign. Considering the radiological findings which indicated the presence of cortical encephalitis, we finally diagnosed the patient to have corticomeningeal encephalitis, with Graves's disease as a co-existing disease.

The HLA type B51 was positive and both the cell counts (predominantly neutrophils) and IL-6 level were elevated in CSF. Therefore, our patient was initially suspected to have neuro-Behçet's disease according to the International Criteria for Behçet's disease (6) and probable neuro-Behçet's disease, as per the International consensus recommendation criteria (7). Two cases of MOG-AD mimicking neuro-Behçet's disease have been reported previously (8). Previous cases showed cerebral and brainstem lesions, whereas the present case showed cortical encephalitis. Although encephalitis in the brainstem or deep subcortical lesions are commonly associated with neuro-Behçet's disease, both of aseptic meningitis and cortical encephalitis are rare manifestation of neuro-Behçet's disease (5). On the other hand, cortical encephalitis has been recognized as a characteristic feature of MOG-AD (3, 9). Our patient was finally diagnosed to have MOG-AD presenting with corticomeningeal encephalitis based on the presence of anti-MOG antibody in serum and

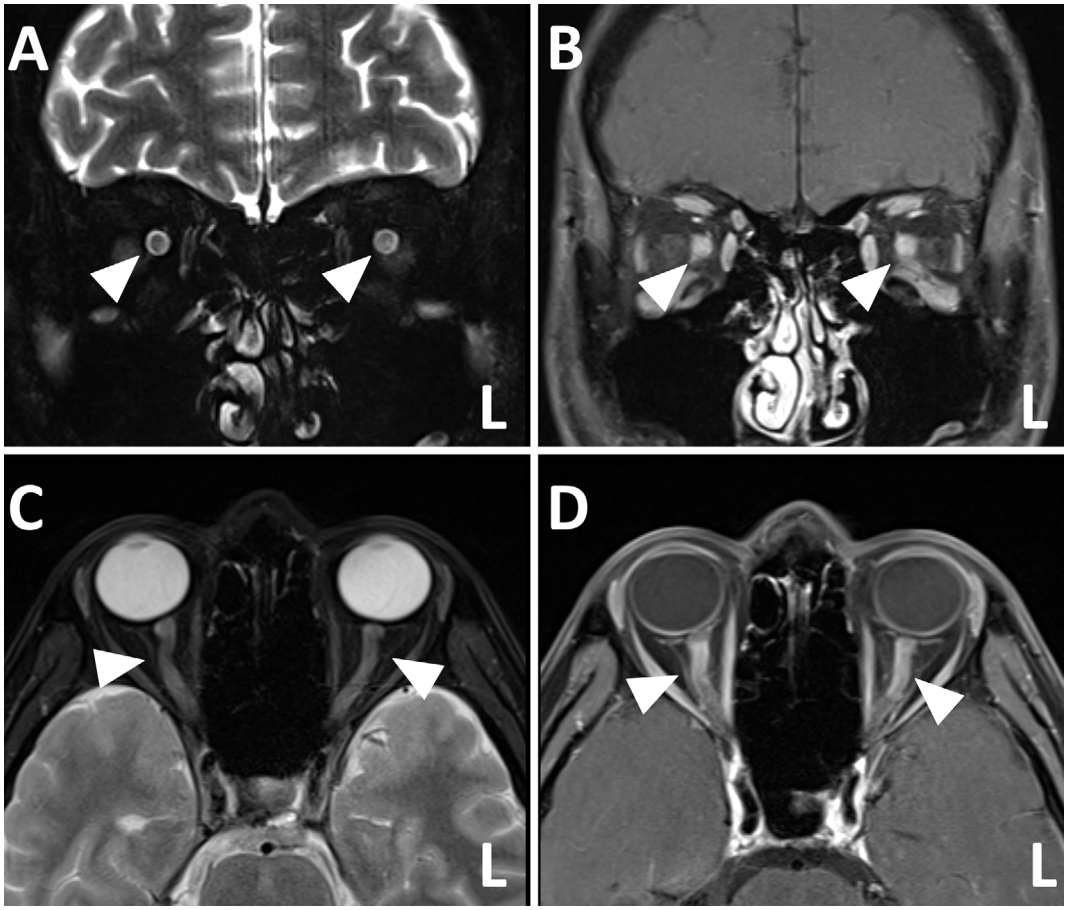

Figure 3. **Magnetic resonance images of the patient. A coronal T2-weighted image showing swelling in the bilateral optic nerves (A) with gadolinium enhancement (B). A horizontal T2-weighted image showing deflection in the bilateral optic nerves (C) with diffuse gadolinium enhancement (D) in the orbital region.**

CSF, characteristic lesion: cortical encephalitis, and a favorable response to steroid therapy. Our findings suggest that MOG-AD may present with clinical and laboratory findings mimicking neuro-Behçet's disease. Therefore, it is important to consider MOG-AD in the differential diagnosis of neuro-Behçet's disease presenting with meningoencephalitis.

To the best of our knowledge, 7 cases of MOG-AD-associated meningitis, which were described to have fever, nausea, and nuchal rigidity, have been reported including our case (Table) (10-16). The mean age of these patients was 24.4 years (range: 3-55); four of these patients were male. Six of these patients had radiological cortical encephalitis, while six of these patients had subcortical lesions. Five of these patients had optic neuritis during their clinical course; however, six of these patients, including our case, either only had meningitis or had meningitis prior to the onset of optic neuritis. Only one patient experienced seizures. All patients had an increase in the cell counts and the total protein level in CSF. Four patients showed a mild decrease in the sugar level (40-60 mg/dL) in CSF. All patients were treated with intravenous steroid therapy and one patient received additional plasma exchange therapy during their clinical course. As maintenance therapy, seven patients were treated with oral steroids and two patients were treated with azathioprine. Three patients (including the present case) experienced a relapse. The clinical characteristics of our patient (increased cell count and total protein in the CSF; steroid-responsive meningitis) were consistent with these cases. Three of these patients (including our case) showed polymorphonuclear cell-dominant pleocytosis in the CSF, and a previous study showed neutrophils which frequently appear in the CSF of patients with MOG-AD during attack (17). These results possibly mean that polymorphonuclear-dominant pleocytosis can be seen during such attacks.

Previously, some types of cerebral cortical encephalitis have been reported (3, 9, 18). One is unilateral cerebral cortical encephalitis (UCCE) (3). UCCE is characterized by seizures and a unilateral radiological abnormality. Interestingly, only one of the cases with MOG-AD presenting with clinical meningitis with radiological cortical encephalitis experienced seizures.

The underlying mechanism for the development of meningitis in MOG-AD is not well characterized. Meningeal involvement may possibly occur as sequelae associated encephalitis because MOG-AD frequently presents with encephalitis. However, one case (16) had only subcortical encephalitis, it possibly means that inflammation spread to the

Table. Clinical Features of MOG-AD Presenting with Meningitis.

Reference	Age Sex	Lesion in cerebrum	CSF Cell (/μL) Mono/Poly (%) Protein (mg/dL) Sugar (mg/dL)	MOG-ab Serum CSF	Treatment acute Chronic	Clinical course
(10)	22 F	1. bilateral cortical 2. bilateral subcortical	57 75/12 121 42	+ -	IVMP PSL	1.meningitis seizure (-)
(11)	28 M	1. bilateral cortical 2. brainstem 3. cerebellum	143 42/54 65 54	+ N.A	IVMP/PE PSL/RTX	1. ON 2. meningitis seizure (-)
(12)	55 F	1. left cortical 2. bilateral subcortical	190 66/N.A 78 N.A	+ N.A	IVMP PSL	1. meningitis 2. ON seizure (-)
(13)	7 F	1. bilateral cortical 2. bilateral subcortical	22 N.A/N.A N.A N.A	1:320 N.A	IVMP PSL/AZA	1. ON 2. meningitis seizure (-)
(14)	6 M	1. bilateral cortical 2. bilateral subcortical 3. brainstem	56 80/20 67.9 Normal	1:5120 N.A	IVMP PSL	1.meningitis seizure (-)
(15)	13 F	1. bilateral cortical 2. bilateral subcortical	150 30/70 52 55	+ N.A	IVMP AZA	1. meningitis 2. ON seizure (+)
(16)	3 M	1. bilateral subcortical	7 N.A/N.A 117 Normal	1:100 N.A	IVMP PSL	1. meningitis seizure (-)
Our case	37 M	1. bilateral cortical	682 37/63 113 47	1:2048 1:64	IVMP PSL	1. meningitis 2. ON

N.A: not available, ON: optic nerve, IVMP: intravenous methylprednisolone, PE: plasma exchange, PSL: prednisolone, RTX: rituximab, AZA: azathioprine

meninges. Another potential mechanism is the spread of inflammation from the meninges to the brain.

Our patient had Graves' disease based on the findings of hyperthyroidism, an increased blood flow in thyroid, and the serum positivity for thyrotropin receptor antibody. MOG-AD is less frequently associated with concomitant systemic autoimmune diseases than aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (19). A few cases of MOG-AD had concomitant Hashimoto encephalopathy (20) and anti-N-methyl-D-aspartate receptor encephalitis (21). Our findings suggest that MOG-AD may also be associated with systemic autoimmune diseases. Further studies are required to elucidate the relationship between MOG-AD and systemic autoimmune diseases.

This case report highlights two important clinical issues. First, MOG-AD can present with meningitis as an initial symptom; therefore, MOG-AD should be considered in the differential diagnosis of meningitis. Second, patients with MOG-AD could also have concomitant systemic autoimmune diseases, such as Graves' disease.

Conclusion

Although MOG-AD has a wide spectrum, the type is gradually being classified. We described a case of MOG-AD presenting with corticomeningeal encephalitis that had concomitant Graves' disease. We should accumulate more MOG-AD cases and describe such cases in detail.

The authors state that they have no Conflict of Interest (COI).

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References

1. López-Chiriboga AS, Majed M, Fryer J, et al. Association of MOG-IgG serostatus with relapse after acute disseminated encephalomyelitis and proposed diagnostic criteria for MOG-IgG-associated disorders. JAMA Neurol **75**: 1355-1363, 2018.
2. Akaishi T, Sato DK, Takahashi T, Nakashima I. Clinical spectrum of inflammatory central nervous system demyelinating disorders

associated with antibodies against myelin oligodendrocyte glycoprotein. Neurochem Int **130**: 104319, 2019.

3. Ogawa R, Nakashima I, Takahashi T, et al. MOG antibody-positive, benign, unilateral, cerebral cortical encephalitis with epilepsy. Neurol Neuroimmunol Neuroinflamm **4**: e322, 2017.

4. Al-Araji A, Kidd DP. Neuro-Behçet's disease: epidemiology, clinical characteristics, and management. Lancet Neurol **8**: 192-204, 2009.

5. Borhani-Haghighi A, Kardeh B, Banerjee S, et al. Neuro-Behcet's disease: an update on diagnosis, differential diagnoses, and treatment. Mult Scler Relat Disord **39**: 101906, 2019.

6. International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol **28**: 338-347, 2014.

7. Kalra S, Silman A, Akman-Demir G, et al. Diagnosis and management of Neuro-Behçet's disease: international consensus recommendations. J Neurol **261**: 1662-1676, 2014.

8. Fujimori J, Takahashi T, Matsumoto Y, et al. Two Japanese cases of anti-MOG antibody-associated encephalitis that mimicked neuro-Behçet's disease. J Neuroimmunol **334**: 577002, 2019.

9. Fujimori J, Takai Y, Nakashima I, et al. Bilateral frontal cortex encephalitis and paraparesis in a patient with anti-MOG antibodies. J Neurol Neurosurg Psychiatry **88**: 534-536, 2017.

10. Nagabushana D, Shah R, Pendharkar H, et al. MOG antibody seropositive aseptic meningitis: a new clinical phenotype. J Neuroimmunol **333**: 476960, 2019.

11. Narayan RN, Wang C, Sguigna P, Husari K, Greenberg B. Atypical anti-MOG syndrome with aseptic meningoencephalitis and pseudotumor cerebri-like presentations. Mult Scler Relat Disord **27**: 30-33, 2019.

12. Suzuki T, Maekawa K, Matsuo K, et al. Aseptic meningitis as an initial manifestation of anti-myelin oligodendrocyte glycoprotein antibody-associated disease. Intern Med **58**: 3319-3321, 2019.

13. Zhong X, Chang Y, Tan S, et al. Relapsing optic neuritis and meningoencephalitis in a child: case report of delayed diagnosis of MOG-IgG syndrome. BMC Neurol **19**: 94, 2019.

14. Leinert J, Neumaier-Probst E, Kutschke G, Tenenbaum T. MOG antibody associated demyelinating syndrome presenting as aseptic meningitis in a 6-year-old boy. Mult Scler Relat Disord **41**: 102050, 2020.

15. Vibha D, Singh RK, Salunkhe M, Dash D, Tripathi M. MOG antibody syndrome presenting as aseptic meningitis: an evolving spectrum. Neurol Sci **42**: 321-323, 2021.

16. Shen W, Zhang Y, Zhou C, Shen Y. Bilateral symmetrical deep gray matter involvement and leptomeningeal enhancement in a child with MOG-IgG-associated encephalomyelitis. BMC Neurol **21**: 10, 2021.

17. Jarius S, Pellkofer H, Siebert N, et al. Cerebrospinal fluid findings in patients with myelin oligodendrocyte glycoprotein (MOG) antibodies. Part 1: results from 163 lumbar punctures in 100 adult patients. J Neuroinflammation **17**: 261, 2020.

18. Fujimori J, Ogawa R, Murata T, Jin K, Yazawa Y, Nakashima I. Unilateral chronic pulsatile headache as the single manifestation of anti-MOG antibody-associated unilateral cerebral cortical encephalitis. J Neuroimmunol **346**: 577322, 2020.

19. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. J Neuroinflammation **13**: 280, 2016.

20. Chen KA, Brilot F, Dale RC, Lafferty AR, Andrews PI. Hashimoto's encephalopathy and anti-MOG antibody encephalitis: 50 years after Lord Brain's description. Eur J Paediatr Neurol **21**: 898-901, 2017.

21. Nan D, Zhang Y, Han J, Jin T. Clinical features and management of coexisting anti-N-methyl-D-aspartate receptor encephalitis and myelin oligodendrocyte glycoprotein antibody-associated encephalomyelitis: a case report and review of the literature. Neurol Sci **42**: 847-855, 2021.