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Short communication

Two Japanese cases of anti-MOG antibody-associated encephalitis that mimicked neuro-Behçet's disease

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ABSTRACT

Recently, we documented two Japanese cases of myelin-oligodendrocyte glycoprotein (MOG) antibody-associated relapsing encephalitis among patients who had been diagnosed with probable neuro-Behçet's disease (NBD). They presented partial systemic BD symptoms, brainstem lesions, and the human leukocyte antigen (HLA) B51 allele and responded well to steroid therapy. Our cases suggest that we need to differentiate anti-MOG antibody-associated encephalitis from probable NBD because both disorders can present with brainstem or cerebral lesions, CSF pleocytosis, and elevated levels of CSF IL-6 and respond to steroid treatment. Furthermore, oral ulceration, skin lesions, and HLA-B51 might be observed nonspecifically in patients with anti-MOG antibody-associated encephalitis.

1. Introduction

Recent studies have shown that anti-myelin oligodendrocyte glycoprotein (MOG) antibodies can be detected by cell-based assays (CBAs) (Jarius et al., 2018) in patients with brainstem encephalitis (Jarius et al., 2016) and cortical encephalitis (Ogawa et al., 2017) (Fujimori et al., 2017) in addition to patients with diseases such as pediatric acute disseminated encephalomyelitis (ADEM), aquaporin-4 (AQP4)-immunoglobulin G (IgG)-negative neuromyelitis optica spectrum disorders (NMOSD), optic neuritis (ON), and longitudinally extensive transverse myelitis (LETM) (Ogawa et al., 2017).

Therefore, we recently tried to assay anti-MOG antibodies by CBA, which has been available since 2014 (Sato et al., 2014), in four patients with a diagnosis of probable neuro-Behçet's disease (NBD) who were in remission under oral steroid therapy because these patients often also present with brainstem lesions. We conducted the live CBA using full-length human MOG transfected HEK 293 with IgG gamma specific secondary antibody. We identified two patients with anti-MOG antibody-associated encephalitis who presented clinical features similar to those of NBD. Here, we report these cases to clarify their clinical features and promote discrimination between the two disorders.

2. Case report

2.1. Case 1

A 55-year-old man experienced focal motor seizures in his left arm in early April 2011. He then gradually realized that he could not extend his left fingers. The patient was admitted to Tohoku Medical and Pharmaceutical University Hospital in mid-April. On admission, monoplegia was observed in the left arm. His body temperature was 36.6 °C, and there were no significant physical findings. Head MRI T2-weighted imaging (T2WI) and fluid-attenuated inversion recovery (FLAIR) images showed multiple high intensity lesions in the right frontal lobe, the subcortical white matter of the left parieto-occipital lobe, the bilateral para-hippocampal gyrus, the left thalamus, the left external capsule, and the left corona radiata. Slight contrast enhancement was observed in the right frontal lobe lesion (Fig. 1, upper panel). Spinal MRI revealed no abnormal findings. A cerebrospinal fluid analysis revealed slightly elevated leukocytes (12 cells/ml; 91% mononuclear cells, 9% polymorphonuclear leukocytes), elevated protein (47 mg/dL), and normal glucose (58 mg/dL). Examinations for infectious central nervous system (CNS) diseases, collagen diseases, and

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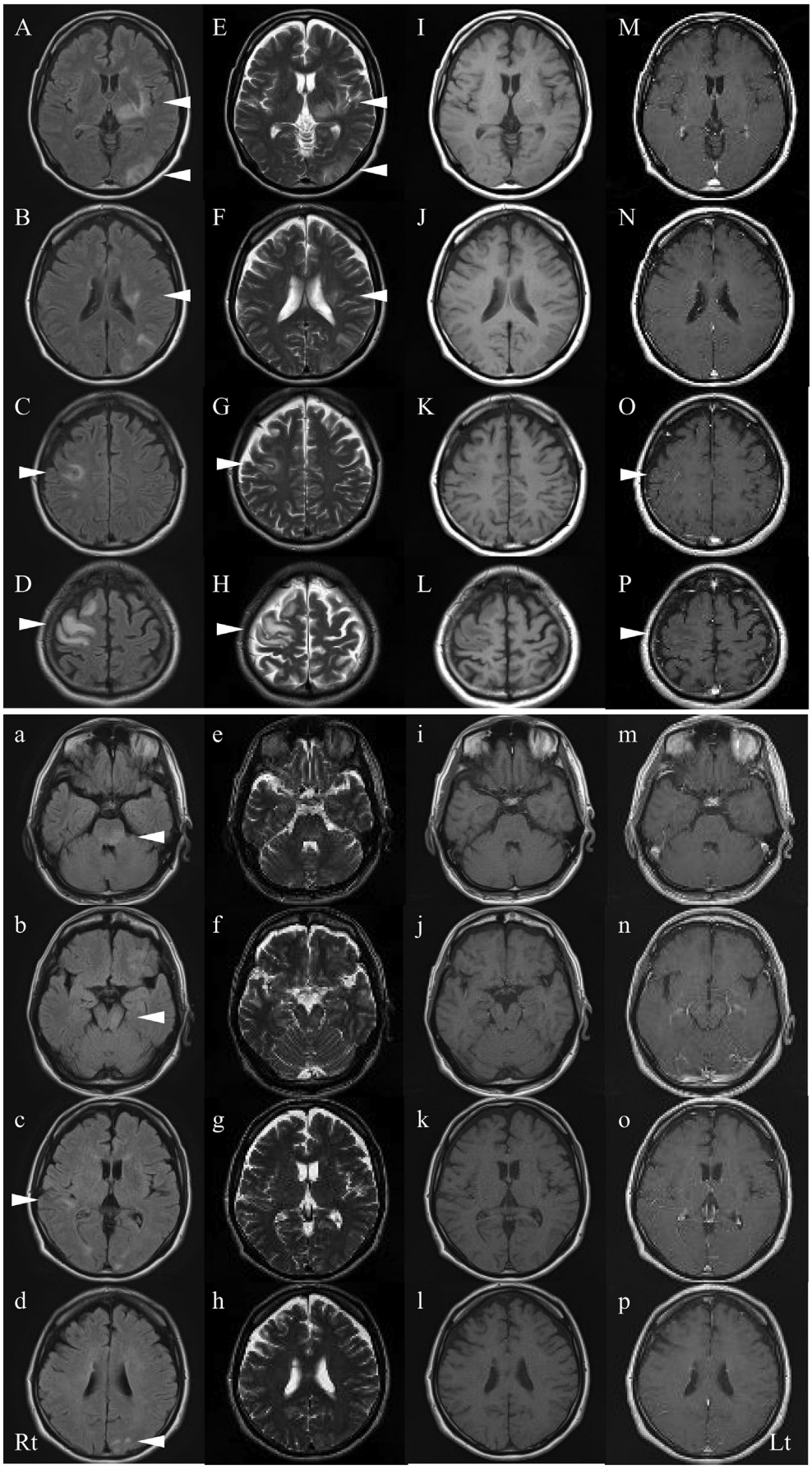

Fig. 1. (Upper panel) Head MRI (Toshiba, 1.5 T) scan showing multiple lesions in the right frontal lobe, the subcortical white matter of the left parieto-occipital lobe, the bilateral para-hippocampal gyrus, the left thalamus, the left external capsule, and the left corona radiata; there was also high signal intensity on fluid-attenuated inversion recovery (FLAIR) (TR 6000 ms, TE 105 ms) (A-D) and T2-weighted images (T2WI) (TR 3800 ms, TE 105 ms) (*E*-H) and slightly low signal intensity on T1-weighted image (T1WI) (TR 600 ms, TE 15 ms) (I-L). Slight contrast enhancement was observed in the right frontal lobe lesion (M-P). (Lower panel) Head MRI on FLAIR (TR 6000 ms, TE 105 ms) (a-d) and T2WI (TR 6800 ms, TE 105 ms) (e-h) showing high signal intensity regions in the right temporal lobe, the left frontal lobe, the left occipital lobe, the left pons, the left midbrain, and the left middle cerebellar peduncle at relapse. No clear contrast enhancement was observed on T1WI (i-p).

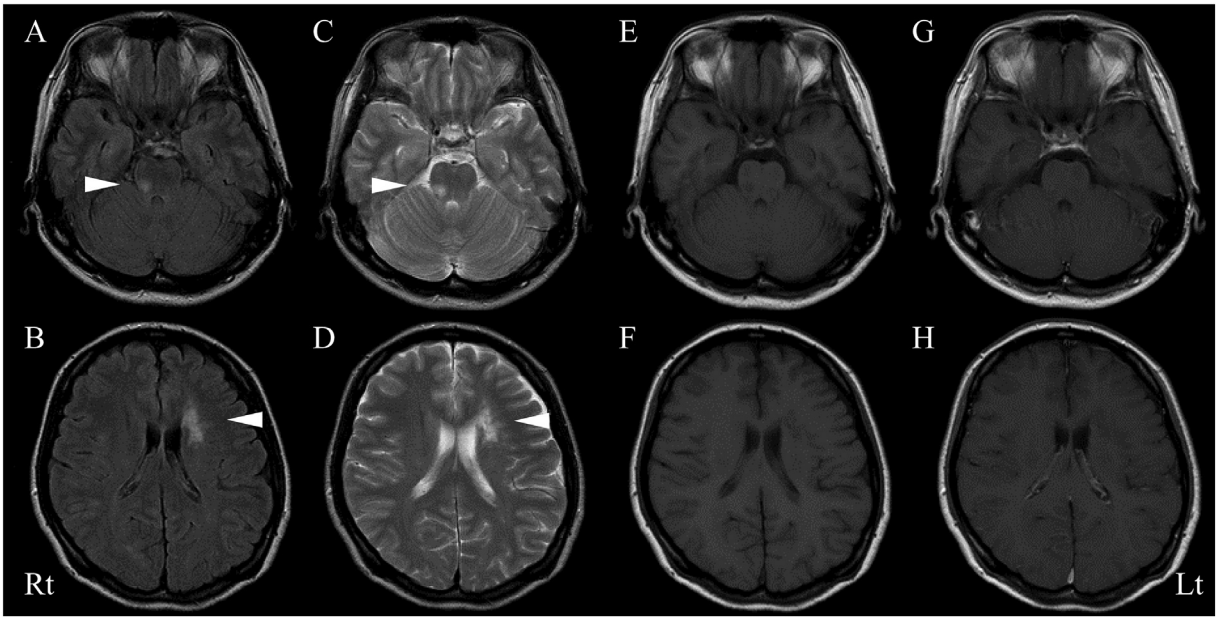

Fig. 2. Head MRI (GE, 1.5 T) FLAIR (TR8000 ms, TE 119 ms) (A) and T2WI (TR 3500 ms, TE 90 ms) (C) showing a high signal intensity lesion in the upper right side of the pons. Head MRI gadolinium-enhanced T1WI (TR 665 ms, TE 14 ms) (G) showing partial contrast enhancement. Head MRI FLAIR (B) and T2WI (D) also showing high signal intensity in the left anterior horn of the lateral ventricle, the left thalamus and the putamen that was considered an old lesion.

Table 1
Comparison of clinical features in two cases of anti-MOG antibody-associated encephalitis.

	Case 1	Case 2
Onset age, sex	55, M	29, F
HLA B	B51	B51
Recurrent oral ulceration	+	+
Recurrent genital ulceration	−	−
Eye lesions	−	−
Skin lesions	+ (Acneiform nodules)	+ (Superficial thrombophlebitis)
Neurological Symptoms at onset	Monoplegia and partial seizure in the left arm	Visual field defect of right eye
at relapse	Cerebellar ataxia in left upper and lower limbs	Abnormal behavior, seizure, right hemiparesis
at second relapse		Saccadic eye movement, Left hemiparesis, hemi-sensory disturbance
Brain MRI lesions at onset	Subcortical white matter, para-hippocampal gyrus, left thalamus- external capsule-corona radiata	Left thalamus - internal capsule - optic tract
at relapse	Subcortical white matter, brainstem, cerebellar peduncle	Left anterior horn of the lateral ventricle to the left thalamus and putamen
at second relapse		Right pons
CSF findings	(At relapse) Cells: 31/ml, protein: 56 mg/dl, IL-6: 245 pg/ml	(At second relapse) Cells: 2/ml, protein: 21 mg/dl
Anti-MOG Ab at onset	ND	Positive (x 128)
at relapse	ND	ND
after relapse	Positive (x 256)	Positive
Response to steroid treatment	Good	Good

ND: not determined

vasculitis were unremarkable. The human leukocyte antigen (HLA) type was B51:01:01.54:01. An ophthalmologic examination showed no significant abnormality. A dermatologic examination showed no abnormality except for acne. Inflammatory CNS disease, including NBD, was suspected, and two courses of high-dose IV methylprednisolone (HIMP) were administered. The patient fully recovered and was discharged in May 2011.

In April 2012, he suffered from headache, pharyngeal pain, and fever. The patient visited our hospital. A physical examination revealed recurrent oral ulceration in the oral cavity, and neurological examination revealed cerebellar ataxia in the left upper and lower limbs. Head MRI on T2WI and FLAIR images showed high signal intensity in the right temporal lobe, left frontal lobe, left occipital lobe, left pons, left midbrain, and left middle cerebellar peduncle (Fig. 1, lower panel). Cerebrospinal fluid (CSF) analysis revealed elevated leukocytes (31 cells/μl; 86% mononuclear cells, 14% polymorphonuclear leukocytes), elevated protein (56 mg/dl), normal glucose (66 mg/dl), and elevated interleukin-6 (IL-6) (245 pg/ml, normal < 4.0 pg/ml) levels. Recurrence of NBD was suspected, and HIMP was administered. Thereafter, the patient recovered and was discharged. Oral prednisolone was continued at 10 mg/day, and no recurrence has since been observed. However, in 2018, our in-house CBA (Sato, Callegaro, 2014) showed that the patient was positive for serum anti-MOG antibodies in 2018 at the timing of remission after relapse (256 x) and negative for anti-AQP4 antibodies.

2.2. Case 2

A 29-year-old woman experienced a right visual field defect in February 2004. The patient was admitted to Tohoku University Hospital. Head MRI T2WI and FLAIR images showed high signal intensity in the left thalamus, internal capsule, and optic tract. There was

relapsing aphthae in the oral cavity, and superficial thrombophlebitis was observed. The HLA type was B51. She was diagnosed with probable NBD and treated with steroid therapy.

The patient was admitted again to the hospital in November 2004 because of the emergence of abnormal behavior, convulsive seizures, and right hemiparesis. Head MRI T2WI showed high signal intensity from the left anterior horn of the lateral ventricle to the left thalamus and putamen. After the administration of HIMP, she recovered. Prednisolone (7.5 mg/day) was administered continuously.

In November 2009, she experienced dysesthesia in the left hand and face and heaviness in the left arm and leg. The patient was readmitted to the hospital in December. Physical findings on admission were a blood pressure of 123/77 mmHg, a pulse of 73 bpm, and a temperature of 36.7 °C. Neurological examination revealed saccadic eye movement, left spastic hemiparesis, and left hemi-sensory disturbance. An ophthalmologic examination verified normal vision, and uveitis was not observed. Head MRI T2WI and FLAIR images showed high signal intensity lesions on the upper right side of the pons (Fig. 2). Spinal MRI revealed no abnormal findings. CSF analysis showed normal results for cell counts (2, all monocytes) and protein (21 mg/dl) and glucose (55 mg/dl) levels. The CSF myelin basic protein (MBP) level was 315 pg/ml (normal < 102 pg/ml). Tests for anti-AQP4 antibody and autoantibodies related to collagen disease and vasculitis were negative. The recurrence of NBD was suspected. After the administration of two courses of HIMP, she recovered. However, in 2018, our in-house CBA (Sato et al., 2014) showed that the patient was positive for serum anti-MOG antibodies during the initial episode in 2004 (128×).

3. Discussion

The two cases presented here were diagnosed with anti-MOG antibody-associated relapsing encephalitis involving the brainstem and cerebrum although they fulfilled the diagnostic criteria for probable NBD. Our cases indicate that anti-MOG antibody-associated encephalitis can mimic probable NBD because both disorders can present with brainstem or cerebral lesions, CSF pleocytosis, and elevated CSF levels of IL-6 (Kaneko et al., 2018) and usually respond well to treatment with steroid therapy. Furthermore, oral ulceration, skin lesions, and HLA−B51, which are part of the typical findings in BD, might be observed nonspecifically in anti-MOG antibody-associated encephalitis.

BD is more prevalent among individuals residing along the ancient Silk Road, including those in countries in the Far East, the Middle East, and the Mediterranean basin (Kalra et al., 2014), and is associated with the major histocompatibility complex HLA−B51, as was found in our cases (Kalra et al., 2014). The International Study Group (ISG) criteria for BD requires the presence of oral ulcerations (aphthous or herpetiform ulceration recurring at least 3 times in one 12-month period) plus any two of the following: genital ulceration, typical defined eye lesions, typical defined skin lesions (erythema nodosum, pseudofolliculitis, papulopustular lesion, or acneiform nodules), or a positive pathergy test (1990). In our cases, case 1 presented recurrent oral ulcerations and acneiform nodules. Case 2 presented with recurrent oral ulcerations and superficial thrombophlebitis, which is one of the characteristic findings of BD (2014) (Sakane et al., 1999).

According to the international consensus recommendation (ICR) criteria for NBD diagnosis (Kalra et al., 2014), a definite NBD diagnosis requires all the following four criteria to be met: satisfying the ISG criteria for BD (Criteria for diagnosis of Behcet's disease, 1990), a neurological syndrome recognized as being caused by BD, the presence of relevant and characteristic abnormalities seen on either or both neuroimaging and CSF, and no better explanation for the neurological findings. Although the brainstem is the typical site of predilection in NBD, isolated cerebral hemisphere lesions can be seen and will need to be differentiated from tumors, abscesses, and congenital cysts. Characteristic CSF findings of NBD include inflammatory changes, such as increased cell counts, increased protein levels, and high IL-6 levels.

Moreover, probable NBD requires one of the following two criteria to be met: (1) a neurological syndrome, such as definite NBD, with systemic BD features but that does not satisfy the ISG criteria; and (2) a noncharacteristic neurological syndrome occurring in the context of ISG criteria-supported BD (Kalra et al., 2014). Therefore, our two cases fulfilled the former diagnostic criteria for probable NBD.

Anti-MOG antibody-associated encephalitis may include ADEM, brainstem encephalitis (Jarius et al., 2016), and cerebral cortical encephalitis (Fujimori et al., 2017; Ogawa et al., 2017), and it may also affect the subcortical white matter (Hamid et al., 2018). Brainstem involvement in MOG-IgG-positive patients has been observed in the pons, medulla oblongata, mesencephalon, and cerebellar peduncles (Jarius et al., 2016). Reflecting the lesion distribution, in MOG-IgG-positive patients, brainstem symptoms have been reported to include respiratory insufficiency, intractable nausea and vomiting, dysarthria, dysphagia, oculomotor nerve palsy, nystagmus, facial nerve paresis, trigeminal hypesthesia/dysesthesia, vertigo, hearing loss, balance difficulties, and gait and limb ataxia (Jarius et al., 2016). In contrast, in NBD, the brainstem lesions usually involve the pons and might extend upwards to involve the midbrain, basal ganglia, and diencephalon (Kalra et al., 2014). Therefore, the involvement of the medulla oblongata or cerebellar peduncles, as observed in case 1, might support a diagnosis of anti-MOG antibody-associated encephalitis rather than NBD (Table 1).

4. Conclusion

The differential diagnosis of NBD is thought to include multiple sclerosis, sarcoidosis, systemic lupus erythematosus, primary Sjogren's syndrome, and primary CNS lymphoma (Kalra et al., 2014). Our cases suggest that in the diagnosis of NBD, we should also differentiate anti-MOG antibody-associated encephalitis.

Declarations of interest

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