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Analysis of clinical features and literature review of myelin oligodendrocyte glycoprotein antibody-associated disease

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Abstract

Objective: The purpose of this study is to analyze the clinical features of myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). *Methods:* A retrospective analysis was conducted on eight patients diagnosed with MOGAD at Anyang City People's Hospital, Henan, China. *Results:* Among the eight patients, five were male and three were female, with an age range of 31 to 68 years and a median age of 46.88 years. Both serum and/or cerebrospinal fluid were tested positive for the MOG antibody. Optic neuritis, myelitis, and cortical encephalitis were among the clinical manifestations. A history of viral infection prior to the onset of the disease (3/8) was observed, and one case also tested positive for the AQP-4 antibody.
Conclusion: Optic neuritis and myelitis are the primary clinical manifestations of MOGAD, while a small percentage of patients also exhibit cerebral encephalitis. Testing for the MOG antibody holds diagnostic significance as the condition is easily misdiagnosed.

Keywords: AQP-4 antibody, cortical encephalitis, MOG antibody, myelitis, optic neuritis

INTROUDUCTION

Myelin oligodendrocyte glycoprotein (MOG) belongs to the immunoglobulin superfamily and is primarily expressed in the central nervous system. Due to its location on the outermost layer of the myelin sheath, high antigenic density, and immunogenicity, MOG is a prominent target for autoimmune disease.[1] With the discovery of MOG antibodies, myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is now considered a distinct class of central nervous system demyelinating diseases.[2] To enhance the understanding of this specific disease category, in this study, we investigated the clinical characteristics of eight patients with MOGAD who were treated at the Department of Neurology at the People's Hospital of Anyang, Henan, China.

METHODS

We collected clinical data from eight adult MOGAD patients who had been diagnosed with MOGAD at the Department of Neurology at the People's Hospital of Anyang between January 2020 and December 2022. The clinical features, laboratory characteristics, and imaging traits of these patients were analyzed.

Diagnostic criteria

All enrolled patients met the MOGAD diagnostic criteria[3]: (1) Core clinical demyelinating event: Optic neuritis, myelitis, acute disseminated encephalomyelitis(ADEM), cerebral monofocal or polyfocal deficits, brainstem or cerebellar deficits, cerebral cortical encephalitis often with seizures; (2) Positive for MOG-IgG in serum and/or cerebrospinal fluid (CSF), as detected by cell-based assay (CBA), with results provided by a third-party medical institution (Kang Sheng Global Medical Center). (3) Exclusion of more appropriate diagnoses including multiple sclerosis.

RESULTS

Among the eight patients, five were male and three were female, with an age range of 31–68 years and a median age of 46.88 years. Three patients (Cases 2, 3, and 4) had a history of viral infection prior to the onset of the disease, while Case 2 have a herpes simplex viral infection.

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All eight patients underwent a comprehensive lumbar puncture examination, with pressures ranging from 90 to 240 mmH2O. The CSF white blood cell count was between 0-280×10^6/L, and the CSF protein level ranged from 231 to 986 mg/L. All eight patients underwent brain magnetic resonance imaging (MRI). Four cases had myelitis as their initial symptoms; of these, three had short-segment lesions (see Figures 1A, 1B, 2A), and one had a long-segment lesion (see Figure 2C). Three cases had optic neuritis as their initial symptoms, and most were unilateral at onset. Two cases presented with abrupt visual loss, while one case experienced retrobulbar neuritis. The ratio of short-segment to long-segment spinal lesions was 3:1 in the four cases where myelitis was the initial symptom. One lesion displayed the classic "H" sign (see Figures 2B, 2D). Moreover, one case, Case 2, involved the brainstem. In Case 2, the ipsilateral brainstem and spinal cord were involved in an inflammatory demyelinating event after the patient had a typical unilateral facial

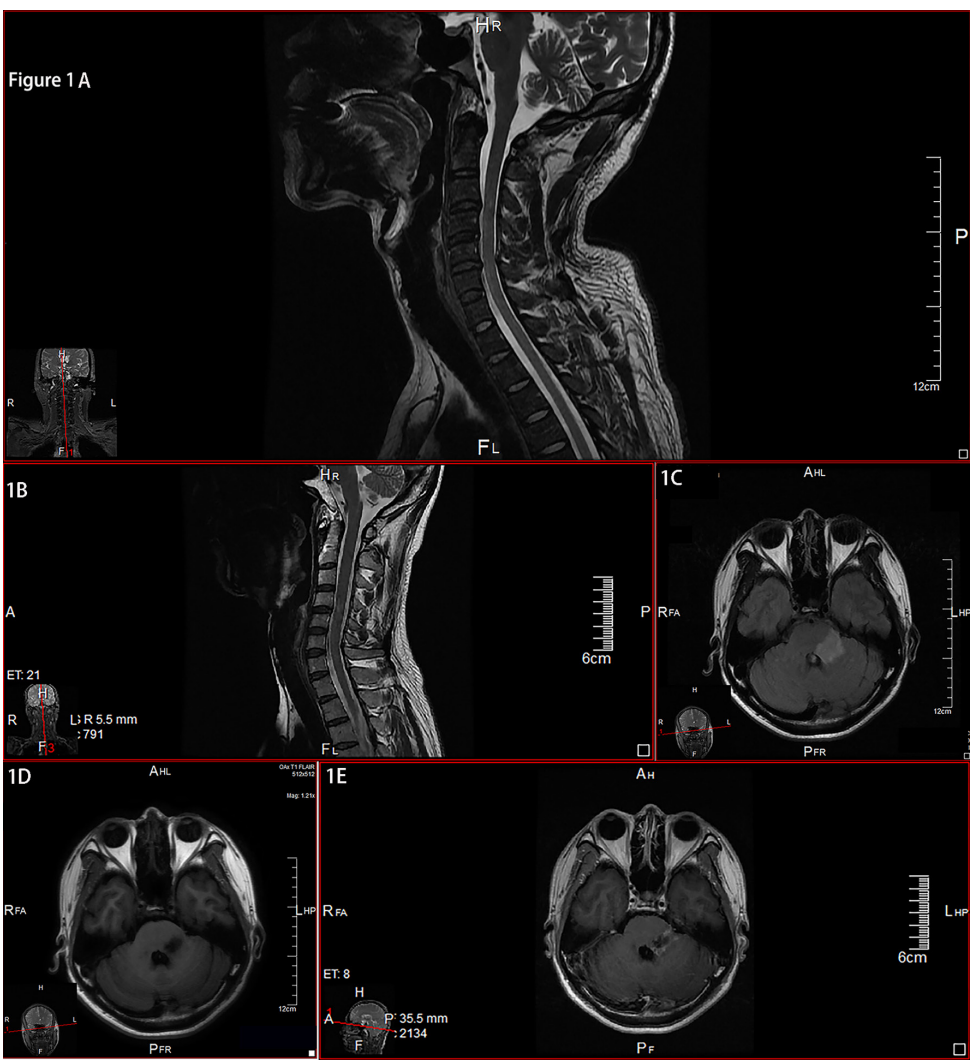

Figure 1. **A**. Cervical spinal cord MRI T2 sequence in sagittal view indicates demyelination signals at cervical spinal cord levels 3, 4, 5, and 6. Lesions are discontinuously distributed and are long-segmented. **B**. Cervical spinal cord MRI T2 sequence in sagittal view shows a demyelination signal at the cervical spinal cord level 5; the lesion is short-segmented. **C**. An axial view of a brain MRI using the FLAIR sequence reveals a demyelination signal at the pons-cerebellar angle but no discernible mass effect. **D**. Brain MRI T1 sequence in axial view shows low signal at the pons-cerebellar angle. **E**. Brain MRI enhanced scan series indicates that the lesion at the pons-cerebellar angle displays ring enhancement, following an open-ring pattern.

herpes simplex virus infection. Corresponding responsible lesions could be seen on MRI (see Figures 1B, 1C, 1D, 1E). There was one case of cortical encephalitis, whose cranial MRI findings are relatively specific: high signal can be observed on T2 FLAIR images, and no evident high signal is visible on DWI (see Figure 3A). One case had cerebellitis (see Figures 3B, 3C), and two cases had optic neuritis, with unilateral lesions. Prolonged visual evoked potential (VEP) latency was observed in patients with optic neuritis. Case 3 initially presented with cortical encephalitis (see Figure 3A) and was diagnosed a month later after developing optic neuritis. Another unusual case was Case 8, whose clinical manifestation was long-segment myelitis (see Figure 3B). Biochemical tests revealed that both serum and CSF were co-positive for MOG antibody and

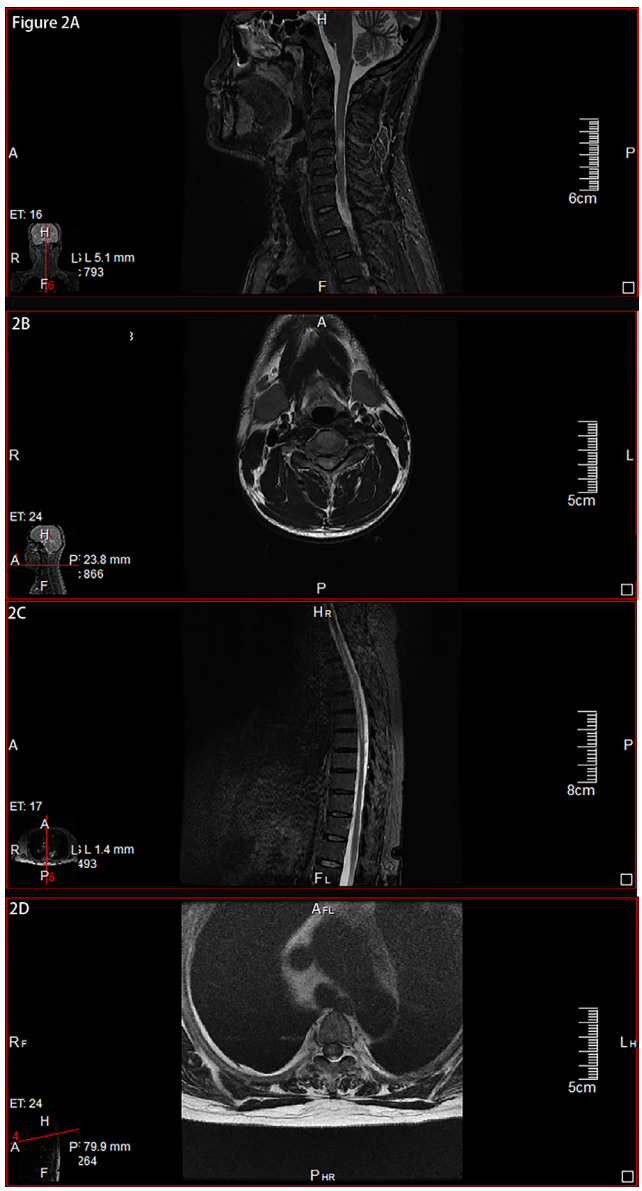

Figure 2. **A**. A demyelination signal is visible in the cervical spinal cord MRI T2 sequence in sagittal view at level 4; the lesion is short-segmented. **B**. An "H"-shaped demyelination signal at cervical spinal level 4 is seen in the cervical spinal cord MRI T2 sequence in axial view. **C**. Demyelination signals are visible at thoracic levels 1–7 in the sagittal view of the thoracic spinal cord MRI T2 sequence. **D**. Demyelination signals with a "H" shape are seen in the thoracic spinal cord MRI T2 sequence in axial view at thoracic levels 1–7.

AQP4 antibody (AQP antibody titers: serum 1:320, CSF 1:10). One of the two patients that tested positive for SS-A52 also tested positive for ANA. Table 1 shows the details of these clinical, CSF and serological information.

DISCUSSION

Optic neuritis, disseminated brain myelitis, neuromyelitis optica, myelitis, and brainstem encephalitis are typical clinical manifestations of MOGAD. In this cohort, optic neuritis (3/8) and myelitis (4/8) were the most frequent initial symptoms. There was also one case of cortical encephalitis, also referred to as FLAIR-hyperintense Lesion in Anti-MOG-associated Encephalitis with Seizures (Flames) syndrome, which manifested initially as seizures and stroke-like symptoms.[4] The primary symptoms include headaches, epilepsy, and cortical symptoms; it often has an acute onset and is localized to one side; and cortical swelling is also a notable feature.[5] It is essential to differentiate this from cytotoxic cerebral edema found in post-epileptic MRI findings. Such patients are often misdiagnosed as having mitochondrial encephalomyopathy or acute cerebral stroke. In this case, the optic neuritis was not definitively diagnosed during the initial episode; instead, it was diagnosed after a subsequent occurrence.

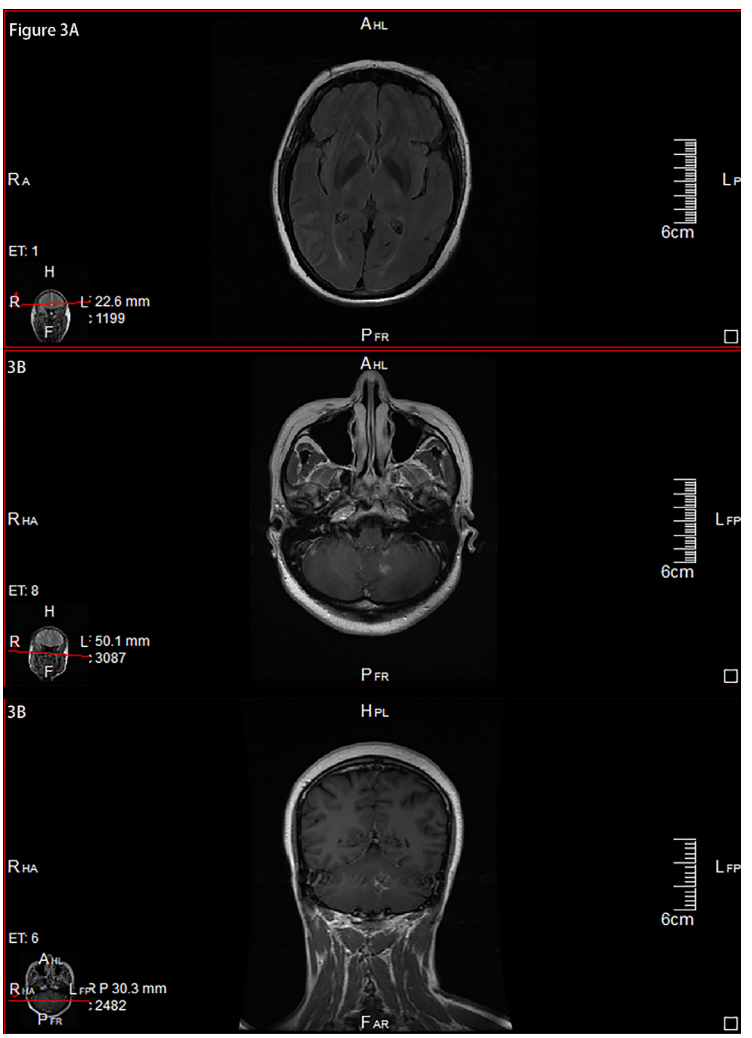

Figure 3. **A**. Right temporal and occipital lobe demyelination signals are seen on brain MRI FLAIR sequence, along with mild cortical edema. **B**. Scattered lesions with partial enhancement are shown in both cerebellar hemispheres in the axial view of a brain MRI enhanced scan series. **C**. Scattered lesions with partial enhancement can be seen in both cerebellar hemispheres in the coronal view of a brain MRI enhanced scan series.

Table 1: Clinical data of patients with MOGADS

Case No.	Gender	Age	Clinical subtype	MOG Antibody titer		Lumbar puncture			EDSS Score		Others
				Serum	CSF	Pressure	Protein	White Blood Cells	Admission	Discharge	
1	Male	41	Myelitis	1:1000	1:10	140	986	280	6.0	2.5	SS-A52+
2	Male	31	Brainstem Encephalitis Myelitis	1:10	1:10	240	556	8	2.0	1.5	ANA+ SS-A52+
3	Female	46	Cortical Encephalitis Optic Neuritis	1:32	1:1	150	408	0	1.0	0	
4	Female	35	Cerebellitis	1:10	1:10	165	326	38	1.0	0	
5	Male	63	Optic Neuritis	1:10	Negative	90	420	2			
6	Male	56	Optic Neuritis	1:10	1:10	140	636	6			
7	Male	35	Myelitis	1:100	1:3.2	135	231	2	1.0	1.0	
8	Female	68	Myelitis	1:10	1:1	150	618	2	8.5	7.0	AQP4 Antibody Positive

Note: Age is expressed in years; CSF pressure is measured in mmH_2O with normal ranges between 80–180 mmH_2O; CSF protein is measured in mg/L with a normal range of 150–450 mg/L; CSF white blood cells are measured in $*10^6$/L with a normal range of 0–$8*10^6$/L. Patients with optic neuritis do not have an EDSS score.

As 20% of patients have a precursor viral infection before the onset of the disease, viral infection is regarded as a peripheral triggering factor for MOGAD.[6] Three of the patients in this group had a clear history of viral infection before symptoms appeared. Case 2 is a typical case of unilateral herpes simplex virus infection on the face, followed by inflammatory demyelination events involving the ipsilateral brainstem and spinal cord, presenting a biphasic course of "onset remission recurrence", particularly similar to viral encephalitis and bimodal encephalitis caused by herpes simplex virus infection.[7] According to studies, MOGAD is linked to demyelinating symptoms after a herpes simplex viral infection, and the lesions are related to the sites of the initial infection. Herpes simplex virus-induced inflammatory responses lead to the breakdown of the blood-brain barrier, allowing peripherally expressed MOG antibodies to enter the central nervous system. Through mechanisms such as "molecular mimicry" and "epitope spreading," MOG antibodies erroneously engage with central antigens, thereby triggering demyelinating events.[8]

Myelitis has a huge spectrum of MRI features, including long-segment, short-segment, or numerous patchy lesions, diffuse damage, and a swollen spinal cord. The majority of lesions are found in the center of the gray matter, and they typically have an "H-shaped" cross-section.[9] Moreover, unlike the spectrum of neuromyelitis optica diseases, it can also affect the lumbar and sacral spinal cord, clinically manifesting as lumbosacral neuritis.

In this cohort, one case was characterized by an initial presentation of cortical encephalitis. However, during the initial hospital admission, the patient declined to undergo a lumbar puncture, hindering the process of arriving at a definitive diagnosis. Subsequently, a month later, the patient experienced a recurrence of optic neuritis, and a lumbar puncture was performed to confirm the diagnosis. This case was also in line with the demyelination recurrence cycle. The MOGAD recurrence cycle has a median duration of five months and a range of one month to four years.[10] An annual relapse rate of 8.3%[11], while the overall relapse rate in adult MOGAD of around 30 - 50%[12,13], underscores the necessity for long-term administration of immunosuppressive agents following the diagnosis of MOGAD to prevent relapses. Specifically, the persistent presence of antibodies can serve as a predictive factor for relapses.[14] Dynamic monitoring of MOG antibody levels and titers has significant implications for

treatment and prognosis.

In one of our cases, the patient was positive for both AQP and MOG antibodies. Due to the high selectivity of humoral immunity, the simultaneous presence of MOG and AQP4 antibodies is exceptionally rare. Merely 7 cases out of 1,520 (0.5%) demonstrated this co-occurrence.[15] This type of patient is considered to be a combination of neuromyelitis optica and multiple sclerosis relapse remitting type, and MOG may have a synergistic effect to drive tissue damage mediated by AQP-4 autoantibodies.[16] This is analogous to the overlapping syndromes of MOGAD and autoimmune encephalitis. Such patients commonly experience severe conditions, multiphasic disease courses, and high annual relapse rates. Clinically, it is recommended to initiate immunosuppressive agents promptly. According to recent case reports, ocrelizumab has shown promising therapeutic efficacy.[17]

In this cohort, optic neuritis was misdiagnosed as anterior ischemic optic neuropathy, cortical encephalitis was mistaken for stroke and mitochondrial encephalomyopathy, and cerebellitis was misdiagnosed as viral encephalitis. To prevent misdiagnoses and missed diagnoses, clinicians need to constantly increase their level of knowledge of MOGAD, given its diverse array of disease patterns. It is anticipated that upcoming clinical research endeavors will pinpoint specific biomarkers associated with MOGAD, facilitating better diagnosis and differential diagnosis.

In conclusion, optic neuritis and myelitis are the primary clinical manifestations of MOGAD, and a small percentage of patients also exhibit cortical encephalitis. The condition is easily misdiagnosed, hence a MOG antibody test is critical for diagnosis.

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DISCLOSURES

Ethics: This study was conducted with approval from the Ethics Committee of An yang People's Hospital (KS-2023-10-23). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Data availability: The data and materials used to support the findings of this study are available upon request.

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Conflict of interest: None

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