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Clinical characteristics and long-term follow-up outcomes of myelin oligodendrocyte glycoprotein antibody-associated disease in Han Chinese participants

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Abstract

Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is an immune-mediated inflammatory demyelinating disease of the central nervous system. This study aimed to delineate the clinical manifestations, imaging features, and long-term outcomes in Chinese patients with MOGAD and analyze the recurrence-associated factors. The phenotypic and neuroimaging characteristics of 15 Han Chinese patients with MOGAD were retrospectively analyzed. Demyelinating attacks, MOG antibodies in the cerebrospinal fluid/serum, response to immunotherapy, follow-up outcomes, and recurrence-associated factors were recorded. The median age at disease onset was 34 years (range, 4–65 years). The most common initial presentations included vision loss (10/15, 66.7%) and seizures (5/15, 33.3%). Serum MOG-Ab titers in 14/15 cases were higher than those in the cerebrospinal fluid and were detected in 3/6 relapsed patients. Brain magnetic resonance imaging during acute attacks showed lesions in 10/15 patients (66.7%), mostly in the cortex/subcortical white matter (5/15, 33.3%). Recurrence occurred in 6/15 patients (40.0%); in 4 patients, recurrence occurred shortly after immunotherapy discontinuation. Residual neurological deficits were present in 5/15 patients (33.3%), including visual impairment, incapacitation, cognitive impairment, and speech reduction. Optic neuritis was the most common clinical manifestation of MOGAD. magnetic resonance imaging findings were heterogeneous and the cerebral cortex/subcortical white matter was the most susceptible brain region. Although patients in the acute phase responded well to methylprednisolone pulse therapy, the long-term recurrence rate was high. Consistently detected serum MOG antibodies and inappropriate maintenance immunotherapy may be associated with recurrence, and residual neurological deficits should not be ignored.

Abbreviations: CNS = central nervous system, CSF = cerebrospinal fluid, IVIG = high-dose intravenous immunoglobulin, MOG = Myelin oligodendrocyte glycoprotein, MOG-abs = MOG antibodies, MOGAD = antibody-associated disease, MP = methylprednisolone, MPPT = methylprednisolone pulse therapy, MRI = magnetic resonance imaging, ON = optic neuritis, WI = weighted imaging.

Keywords: long-term outcome, magnetic resonance imaging, myelin oligodendrocyte glycoprotein antibody-associated disease, optic neuritis, recurrence

WZ, LY, JW, LC and MH contributed equally to this work.

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Approval was obtained from the Medical Ethics Committee of Liuzhou People Hospital (No. KY2022-006-1). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Informed consent was obtained from legal guardians.

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1. Introduction

Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is an immune-mediated inflammatory demyelinating disease of the central nervous system (CNS).[1] MOGAD is an immune-pathogenetically distinct entity from multiple sclerosis and aquaporin-4 (AQP4)-immunoglobulin (Ig) G-positive neuromyelitis optica spectrum disorder.[2] The clinical and neuroimaging manifestations of MOGAD are heterogeneous, ranging from isolated optic neuritis (ON) or myelitis to multifocal CNS demyelination, often in the form of acute disseminated encephalomyelitis or cortical encephalitis. Genetic and environmental factors may be important determinants of clinical phenotypes and disease progression.[3] Although no age group is exempt, the median age of onset is within the fourth decade of life.[4] Approximately 50% of patients have a relapsing course,[5] and residual disability develops in 50% to 80% of patients.[4]

The clinical features, long-term outcomes, and associated influencing factors of MOGAD in China are unclear. Most patients in these studies were children[4,6,7] or cases of MOGAD with ON.[8,9] Thus, this study aimed to delineate the clinical manifestations, imaging features, and long-term outcomes in Chinese patients (especially for adults) with MOGAD and analyze the factors associated with disease recurrence.

2. Methods

The study was approved by the Medical Ethics Committee of Liuzhou People Hospital (No. KY2022-006-1). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Informed consent was obtained from the patients or legal guardians.

2.1. Aim and study design

Considering the high recurrence and disability rates of MOGAD, we analyzed the disease characteristics in 15 patients in southern China, with the aim of improving its management efficacy. This study retrospectively analyzed the data of 15 patients newly diagnosed with MOGAD at the (blinded for review) between January 2016 and January 2020.

2.2. MOGAD criteria

We analyzed the demographic and clinic characteristics of each patient including sex, age, clinical manifestations, serum and cerebrospinal fluid (CSF) antibodies, electroencephalogram, neuroimaging, treatment, and long-term outcomes.

MOGAD was diagnosed according to the following diagnostic criteria[1]: serum MOG-IgG-positive, detected by cell-based assay with full-length human MOG as the target antigen; clinical manifestations, including one or more of the following: ON, including chronic relapsing inflammatory ON; transverse myelitis; encephalitis or meningoencephalitis; or brain stem encephalitis; magnetic resonance imaging (MRI) or electrophysiology findings (visually evoked potential of isolated ON) associated with CNS demyelination; and other diagnoses that could explain the illness were ruled out.

Criteria for MOGAD recurrence were defined as follows: worsening of the preexisting clinical symptoms or new-onset of neurological symptoms or signs that appear after the acute phase; neuroimaging may show new-onset responsible lesions; ineffective immunotherapy; and the condition is difficult to explain by other etiologies.

2.3. MOG-antibodies detection method

MOG antibodies (MOG-Abs) and AQP4 antibodies were detected by a cell-based assay (Guangzhou Jinyu Medical Laboratory, Guangzhou, China). We previously confirmed that the detection method for MOG-Abs is reliable.[10,11] The cutoff value for being MOG positive in the commercial assay was a titer of 1:10.

2.4. Immunotherapy

Immunotherapy included the following modalities:

Methylprednisolone pulse therapy (MPPT): Adult patients were administered intravenous methylprednisolone (MP) sodium succinate (Pfizer Manufacturing Belgium NV, Puurs-Sint-Amands, Belgium) 1 g/day for 5 days, followed by 0.5 g/day for 3 days and 0.25 g/day for 3 days thereafter, before switching to oral steroid hormones (MP; Tianyao Pharmaceutical Co., LTD., Tianjin, China; 0.8 mg/kg/day) or prednisone acetate (PED; Xianju Pharmaceutical Co., Ltd., Zhejiang, China; 1 mg/kg/day). This dose was gradually reduced by 1 tablet per week (MP, 4 mg per tablet; PED, 5 mg per tablet) until the patient received 2 tablets per day. This dose was maintained for 4 months. Pediatric patients received intravenous MP (20~30 mg//kg/day) for 3 to 5 days and were then tapered to oral prednisone acetate (1 mg/kg, similar to the adult patients who were tapered off within 3–6 months).

Intravenous gamma globulin (Taibang Biological Products Co., Ltd., Guizhou, China; 0.4 g/kg/day) for 5 days.

Other immunotherapies included oral azathioprine (Shanghai Xinyi Pharmaceutical Co., Ltd., Shanghai, China), mycophenolate mofetil (MMF; Zhongmei Huadong Pharmaceutical Co., Ltd., Hangzhou, Zhejiang, China), and methotrexate (Shanghai Xinyi Pharmaceutical Co., Ltd).

3. Results

The median age at disease onset was 34 years (range, 4–65 years). Eight patients were male and 7 were female (Table 1).

Seven patients had a history of prodromal infection. The most common clinical symptoms were impaired vision (10/15, 66.7%), epilepsy (5/15, 33.3%), and limb weakness or numbness (4/15, 26.7%). Mental abnormality, walking instability, and cognitive decline were observed in 2, 2, and 1 patient, respectively. Four of the 10 patients with impaired vision (40%) also experienced oculomotor nerve paralysis, and 5 (50%) had concurrent impaired vision in both eyes. One patient felt eye distension and pain, and another had visual field loss. MOGAD patients with disease relapse were more prone to recurrence of visual impairment (5/6, 83.3%).

3.1. Laboratory findings

MOG-Abs were detected in the serum and CSF of all patients. The CSF pressure was elevated (reference range: <180 mmH_2O) in 2/15 cases. CSF analysis showed an increased white blood cell count in 2/15 patients and increased protein concentrations in 4/15 cases. Normal CSF sugar and chloride contents were noted. Three of the 15 cases were positive for CSF MOG-Ab. The serum MOG-Ab titers in 14 cases were higher than in the CSF. AQP4 antibody was detected in 2 cases (MOG-Ab was identified as the responsible antibody). Serum MOG-Abs remained detectable in 3/6 relapsed patients, and the titer was almost the same as that at the initial presentation.

3.2. Electroencephalogram finding

Electroencephalogram was performed in 12/15 patients, showing no abnormalities in 5, mild abnormalities in 6, and mild-to-moderate abnormalities in 1 patient. Four patients had seizures, with 2 showing spikes/sharp waves in their electroencephalograms, while the other 2 had normal electroencephalograms.

Table 1

Demographics, clinical features, main therapy, and long-term follow-up outcomes of Cases with MOG-antibody-associated disorders.

	Age/ Sex	Prodromal symptoms	Neurological symptoms and signs	MOG-Ab in CSF/ Serum	CSF*,† analysis	EEG	MRI	Acute therapy	Maintenance therapy‡,§	Relapses	Long-term follow-up outcomes	VEP or OCT
Case 1	52 Y/F	Headaches	Limb weakness, unsteady gait, positive Romberg sign, dysarthria, dysphagia	1:10/1:10; Serum MOG-Ab 1:32 in the relapse	CSF protein 0.61 g/L	Mild abnormality	Hyperintense signal on T2WI/FLAIR/ADC and hypointense signal on T1WI in the brainstem, left cerebellum, right temporal lobe, corpus callosum; the hyperintense MRI signal weakened 15 d later. optic nerve MRI: (–)	MPPT and high-dose IVIG	Low-dose MP and AZA for 30 Ms	4 Ms after discharge	Symptoms were relieved at 30 Ms	None
Case 2	48 Y/M	Fever	Acute cognitive impairment, slow response, slight neck rigidity, increased muscle tone in the extremities	Negative/1:10	No abnormality	Roughly normal EEG	Initial MRI showed hyperintense signal on T2WI/FLAIR and hypointense signal on T1WI in the brainstem, hypothalamus, and hippocampus. One mo later, the hyperintense MRI FLAIR signal in the brainstem disappeared	MPPT and high-dose IVIG	MP 48 mg/d, tapered off to 16 mg/d, maintained for 1 Y	None	Cognitive impairment, slow response, and needs assistance with activities of daily living at 25 Ms	None
Case 3	27 Y/F	None	Repeated impaired vision and hypomnesis, convulsions, increased muscle tone in extremities; positive bilateral ataxia signs	Negative/1:10	No abnormality	Mild abnormality	Hyperintense signal on T2WI/FLAIR and hypointense signal on T1WI at the bilateral cerebellar hemispheres, frontotemporal, and left parietal lobes, without diffusion restriction	MPPT	MP 40 mg/d, tapered off, low dose for 6 Ms	Cognitive decline after MP therapy discontinuation, however improved after rehospitalization	Incapacitation and poor verbal ability at 26 Ms	None
Case 4	29 Y/M	Headache and fever	Impaired vision in right eye, convulsions	Negative/1:32; Serum MOG-Ab 1:32 in the 2nd relapse	No abnormality	Roughly normal EEG	MRI showed hyperintense signal on FLAIR in a sulcus in the right frontotemporal lobe, and right optic nerve thickening with uniform enhancement	MPPT	Low-dose PED for 6 Ms, initial methotrexate 15 mg/W, followed by 12.5 mg/d after the 2nd relapse	One mo after PED discontinuation, and again after 4 Ms	Improved vision at 27 Ms	None
Case 5	29 Y/M	Low-grade fever and headache	Impaired vision, convulsions, slight neck rigidity, disappearance of pupillary light reflex in the right eye	Negative/1:32	CSF WBC, 264×10^6/L; protein 0.954 g/L	Mild abnormality	Initial MRI showed hyperintense signal on FLAIR in the corpus callosum; 3 Ms later, the hyperintense MRI signal nearly disappeared	MPPT	Low-dose PED for 6 Ms, MMF for 8 Ms	None	Normal vision and daily activity at 32 Ms	None

(*Continued*)

Table 1
(Continued)

	Age/ Sex	Prodromal symptoms	Neurological symptoms and signs	MOG-Ab in CSF/ Serum	CSF*,† analysis	EEG	MRI	Acute therapy	Maintenance therapy‡,§	Relapses	Long-term follow-up outcomes	VEP or OCT
Case 6	43 Y/M	Coughs, nasal obstruction	Decreased vision in the right eye, weakness and numbness of the lower limbs	1:32/1:100	CSF pressure 180 mmH_2O, protein 804.6 mg/L	Mild abnormality	Initial brain, optic nerve, and cervicothoracic spine MRI showed hyperintense signal on T2WI and equisignal on T1WI at C3–4. Thoracic spine MRI: (–); 6 Ms later, the hyperintense MRI signal at C3–4 disappeared	MPPT	PED 60 mg/d, tapered off, then low dose for 18 Ms; AZA 100 mg/d after the 1st relapse, and maintained for 25 Ms	3 Ms after the 1st episode, and again after another 3 Ms	Poor right-eye vision at 36 Ms	VEP at the 1st episode showed right optic nerve damage
Case 7	65 Y/F	None	Impaired vision in both eyes, droopy right upper eyelid, sluggish, diminished pupillary light reflex in the right eye with impaired adduction	Negative/1:32	CSF pressure 200 mmH_2O, protein 1009.6 mg/L	Mild abnormality	MRI 1 mo after onset showed a small syringomyelia and encephalanalosis; cervical spine MRI: (–)	MPPT	Initial PED 55 mg/d, tapered off, then low dose for 18 Ms with AZA for 44 Ms	None	Impaired right-eye vision at 44 Ms	16 Ms later, VEP showed amplitude reduction in right eye. OCT showed thinning of PRNFL in left eye
Case 8	35 Y/F	None	Repeated impaired vision in the right eye, convulsions	Negative/1:32	No abnormality	No abnormality	Brain and optic nerve MRI showed slightly thickened right optic nerve	MPPT and MMF	Low-dose MP for 10 Ms, MMF for 33 Ms	2 Ms after MP discontinuation	Slightly decreased vision at 33 Ms	None
Case 9	4 Y/F	None	Decreased vision in both eyes with right gaze palsy	Negative/1:100; serum MOG-Ab: 1:100 in the 1st relapse	CSF protein 212.1 mg/L	No abnormality	Initial MRI showed multiple intracranial foci. Cervicothoracic spine MRI: (–). Two yr later MRI showed hyperintense signal on T2WI and hypointense signal on T1WI at the bilateral frontotemporal lobes; 8 Ms later, MRI showed that the foci nearly disappeared	MPPT	MP tapered off, followed by low-dose MP for 1 yr; long-term maintenance with AZA 50 mg/d	7 Ms after initial hospitalization, and 2nd 3 Ms after immunotherapy discontinuation	Improved vision 64 Ms after the 1st onset	None
Case 10	16 Y/F	Low-grade fever, general fatigue	Raving, drowsiness, disappearance of pharyngeal reflex	Negative/1:10	CSF protein 352.3 mg/L	Mild-to-moderate abnormality	Initial MRI showed abnormal signals in the medulla oblongata; 6 Ms later, MRI showed abnormal signals in the area postrema, left basal ganglia, and around the third ventricle; 30 Ms later, MRI showed softening foci in the basal ganglia and area postrema	MPPT and AZA	Initial PED 60 mg/d, tapered off, low dose for 24 Ms and AZA for 48 Ms	None	Resumed good general condition at 48 Ms	None

(*Continued*)

Table 1
(Continued)

	Age/ Sex	Prodromal symptoms	Neurological symptoms and signs	MOG-Ab in CSF/ Serum	CSF*,† analysis	EEG	MRI	Acute therapy	Maintenance therapy‡,§	Relapses	Long-term follow-up outcomes	VEP or OCT
Case 11	41 Y/F	None	Dizziness, walk unsteadily, positive Romberg sign, left sided positive finger-nose test	Negative/1:10	No abnormality	No abnormality	Brain and cervicothoracic spine MRI: (–). Optic nerve MRI showed bilateral optic nerve swelling.	MPPT	Without immunotherapy	None	Freedom of movement at 40 Ms	None
Case 12	27 Y/M	Cold symptoms	Limb numbness, decreased muscle strength in lower extremities, increased muscle tone in the extremities, bilateral positive Babinski sign	1:10/1:32	CSF WBC 82×10^6/L	Not done	MRI showed hyperintensity on T2WI and isointense signal on T1WI at C3–6. Brain and thoracic spine MRI: (–)	MPPT	Initial PED 60 mg/d, tapered off, low dose for 6 Ms; MMF 0.5 g/d for 18 Ms	None	Return to normal life and work at 29 Ms	None
Case13	22 Y/M	None	Left eye swelling with impaired vision, limited outreach in both eyes	Negative/1:10	No abnormality	Mild-to-moderate abnormality	Brain, optic nerve, and cervicothoracic spine MRI: (–)	MPPT	Initial PED 60 mg/d, tapered off, low dose for 1 yr	None	Near complete vision recovery at 37 Ms	None
Case 14	6 Y/M	None	Decreased vision in both eyes	Negative/1:10	No abnormality	Not done	Brain MRI: (–)	MPPT	Initial PED 60 mg/d, tapered off, low dose for 6 Ms	None	Return to normal vision at 36 Ms	None
Case 15	32 Y/M	None	Decreased vision in both eyes, visual field defect in the right eye	Negative/1:32	No abnormality	Not done	Brain, optic nerve, and cervicothoracic spine MRI: (–)	MPPT	Initial PED 60 mg/d, tapered off, low dose for 9 Ms, MMF 1 g/d for 11 Ms	None	Good vision recovery at 24 Ms without affecting normal work	VEP: P100 latency with moderate amplitude reduction in right eye, and severe amplitude reduction in left eye. 1 yr later, OCT: thinning of PRNFL in both eyes

(–) = no abnormality, ADC = apparent diffusion coefficient, AZA = Azathioprine, C = cervical vertebra, CSF = cerebrospinal fluid, EEG = Electroencephalogram, F = female, FLAIR = fluid-attenuated inversion-recovery, IVIG = intravenous immunoglobulin, M = male, MMF = mycophenolate mofetil, MOG = myelin oligodendrocyte glycoprotein, MOG-Ab = myelin oligodendrocyte glycoprotein antibody, MP = methylprednisolone, MPPT = methylprednisolone pulse treatment, MRI = magnetic resonance imaging, Ms = months, OCT = optical coherence tomography, PED = prednisone, PRNFL = peripapillary retinal nerve fiber layer, VEP = Visual evoked potential, W = week, WBC = white blood cell, WI = weighted imaging, Y = year, Yrs = years.

*CSF protein reference range: 150–450 mg/L.

†CSF WBC reference range: 0–8 × 10^6/L.

‡Tapered off, decrease of prednisone by 5 mg/wk or methylprednisolone by 4 mg/wk.

§Low dose, 5–10 mg/d prednisone or 4 mg/d methylprednisolone.

3.3. Neuroimaging findings

Brain, cervical-thoracic vertebra, and orbital MRIs were performed for 15, 10, and 7 patients, respectively. Acute lesions were widely distributed, including in the medulla oblongata (Fig. 1A), dorsal or lateral pons (Fig. 1B, E, H), cerebral peduncle and midbrain (Fig. 1C, D, F, G), areas surrounding the third ventricle (Fig. 1I), bilateral frontal lobe (Fig. 1K and L), bilateral temporal lobe (Fig. 1M), basal ganglia (Fig. 1K), corpus callosum (Fig. 1O), cervical spinal cord (Fig. 1P–T), and optic nerve (Fig. 1U). The most common lesion locations in the brain were the cortical and subcortical white matter (5/15, 33.3%), limbic lobe (4/15, 26.7%), brainstem (4/15, 26.7%), optic nerve (3/15, 20%), cervical medulla (2/10, 20%), and corpus callosum (1/15, 6.7%).

The MOGAD lesions appeared hyperintense on T2-weighted imaging (WI; Fig. 1C), fluid-attenuated inversion recovery (Fig. 1A and B), and apparent diffusion coefficient (Fig. 1D), isointense or slightly hyperintense on diffusion-WI (Fig. 1F), and hypointense on T1WI (Fig. 1E). Some lesions showed partial nodular enhancement (Fig. 1G) or no enhancement at all.

The acute lesions had many forms, including single or multiple (Fig. 1K and L), symmetric or asymmetric (Fig. 1N and O), patchy, or irregularly shaped. Large lesions appeared similar to tumors (Fig. 1V and W), with the invasion of several lobes, while small lesions were occasionally confined to the sulci in the frontal lobe (Fig. 1N). A diseased optic nerve had the potential to become thick (Fig. 1U).

In the spinal cord, short-segmental lesions were relatively common (Fig. 1R) and axial MRI showed patchy unilateral lesions (Fig. 1S). The abnormal signal within the lesions was evidently reduced or had even completely disappeared after immunotherapy (Fig. 1J), and slight brain atrophy was observed at the original lesion sites on follow-up MRI (Fig. 1X).

3.4. Treatment and outcomes

MPPT was provided as acute therapy to 14 of 15 patients during hospitalization. Of these, 2 also received high-dose intravenous immunoglobulin (IVIG), 1 received oral azathioprine,

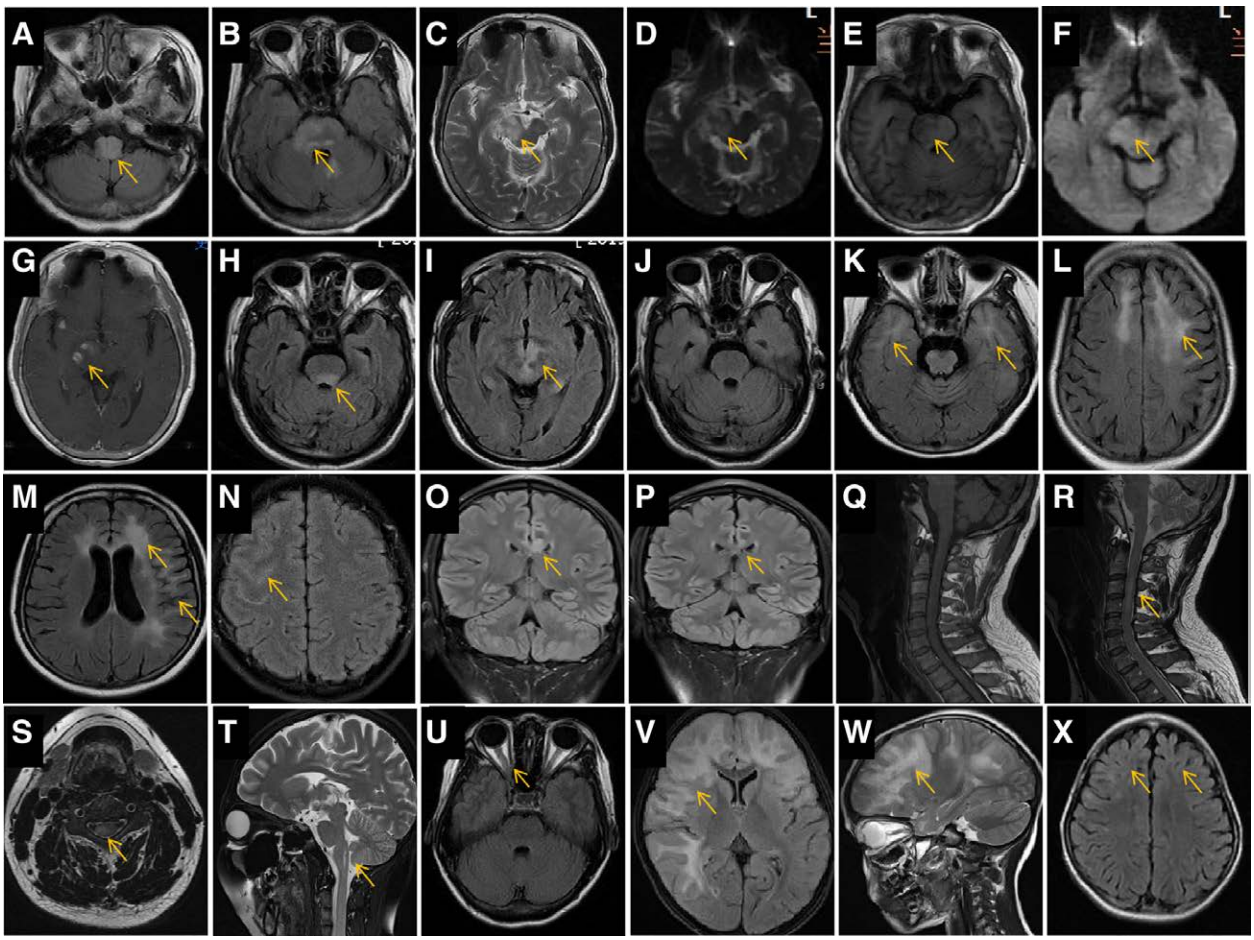

Figure 1. Characteristics and lesion evolution in brain magnetic resonance imaging (MRI) of representative cases. •Patient 1. Initial brain MRI showing hyperintense regions in the bilateral medulla oblongata (A, arrow), pons (B, arrow), right pedunculus cerebri, and right midbrain (C, arrow) on fluid-attenuated inversion recovery (FLAIR, A and B, arrows), T2-weighted imaging (WI, C, arrow), and apparent diffusion coefficient (D, arrow), hypointense on T1WI (E, arrow), and without diffusion restriction on diffusion-weighted imaging (DWI, F). Several spot-like enhanced lesions are noted in the right pedunculus cerebri (G, arrow). •Patient 2. Initial MRI showing hyperintense regions in the bilateral dorsal pons (H, arrow), midbrain, and areas around the third ventricle (I, arrow) on FLAIR. The hyperintense signal in the brainstem FLAIR disappeared 1 mo later (J). •Patient 3. FLAIR MRI showing a hyperintense signal in the bilateral temporal poles (K, arrow), frontal white matter regions (L, arrow), anterior horns of the lateral ventricle (M, arrow), and cortical and subcortical regions in the left temporal lobe (M, arrow). •Patient 4. FLAIR MRI showing a hyperintense signal in the right frontotemporal lobe sulcus (N, arrow). •Patient 5. Initial FLAIR MRI showing a hyperintense signal in the corpus callosum body (O, arrow); the hyperintense signal nearly disappeared on MRI 3 mo later (P, arrow). •Patient 6. Initial sagittal T1WI MRI of the cervical spinal cord showing isointense signal (Q, arrow) and short, segmental hyperintense signal in the sagittal (R, arrow) and axial (S, arrow) T2WI. •Patient 7. MRI 1 mo after onset showing a small syringomyelia (T, arrow). •Patient 8. Brain MRI showing slight thickening of the right optic nerve (U, arrow). •Patient 9. MRI showing a large hyperintense area on T2WI in the bilateral frontotemporal lobes, mimicking a tumor (V and W, arrow); MRI performed 8 mo later showed that the abnormal signals nearly disappeared, with slight brain atrophy (X, arrows).

and 1 received oral MMF. Active immunotherapy alleviated their symptoms.

Maintenance therapy after discharge comprised oral PED in 9 patients, among whom 3 received oral PED alone, 3 received azathioprine, 2 received MMF, and 1 received methotrexate. Five patients received oral MP after discharge, of which 2 received oral MP alone, 1 received azathioprine, and 1 received MMF. One patient received purely symptomatic treatment.

3.5. Long-term follow-up findings

The median time from the initial onset to the last follow-up assessment was 34.6 months (range, 24–64 months). Nine symptom recurrences in 6 patients were noted (40%). Of these, 4 recurrences occurred shortly after the steroid hormone was discontinued. Residual neurological deficits were evident in 5 of the 15 patients (33.3%), and manifested as visual impairment in 4, incapacitation in 2, cognitive impairment in one, and speech reduction in 1 patient.

4. Discussion

Our findings revealed that ON is the most common clinical manifestation of the first episode and in recurring MOGAD in Chinese patients. MOGAD presented highly heterogeneous MRI findings. The cerebral cortex and subcortical white matter were the most susceptible brain regions, followed by the limbic lobe and optic nerve. Patients in the acute phase responded well to MPPT; however, the long-term recurrence rate was high, and one in every 3 patients had residual neurological deficits.

4.1. Initial clinical manifestations of MOGAD

The current results indicate that ON was the most common manifestation of MOGAD, followed by epilepsy and limb weakness/numbness. Cognitive decline, psychiatric disorders, slurred speech, and unsteady gait may also occur. The disease course can be monophasic or relapsing, with subsequent relapses most commonly involving the optic nerve.[1] Functional blindness in one or both eyes was noted during at least 1 ON episode in approximately 70% of the patients.[12] Half of our patients had impaired vision with simultaneous presentation in both eyes. MOGAD typically presents with isolated ON (55%, bilateral in almost half of these cases), transverse myelitis (18%), or acute disseminated encephalomyelitis-like (18%).[2] Both children in our study had visual impairment as the initial symptom. Visual loss is reportedly common in children with MOGAD.[7] Isolated ON was the most frequent clinical presentation in both children and adults, and acute disseminated encephalomyelitis syndrome was more frequent in children than adults.[13] One study[6] reported that, at the onset, ADEM was the most common clinical phenotype in children, followed by isolated ON or NMOSD. Notably, the clinical presentation of MOGAD changes with age.[14] Impaired vision in our patients was often accompanied by oculomotor nerve paralysis; 1 patient felt eye distension and pain and another experienced visual field loss. Patients with ON often complain of ocular, ocular rotation, or orbital pain or acute loss of vision in one or both eyes, visual field defects, changes in color vision, or decreased contrast sensitivity during the acute phase.[5] Optical coherence tomography in our patients showed obvious thinning of the peripapillary retinal nerve fiber layer after the acute episode, which may be the cause of the impaired vision. Patients with MOG-associated ON show varying degrees of atrophy of the peripapillary retinal nerve fiber layer and macular ganglion cell-inner plexiform layer 6 months after disease onset,[8] which could be the reason for the observed residual visual deficit. Seizures and encephalopathy occur frequently in patients with MOGAD and are often associated with cortical and subcortical brain lesions.[15]

4.2. Relapsing clinical manifestations of MOGAD

Our results showed that patients with MOGAD had a high recurrence rate (40%) and that 4 of the 9 (44.4%) relapses occurred shortly after discontinuing steroid hormone treatment. A French nationwide adult cohort study[16] showed that the probability of encountering the first relapse after 2 and 5 years was 44.8% and 61.8%, respectively, indicating that longer observation time is associated with higher recurrence rates. Treatment failure leading to the rapid development of disability and flare-ups after steroid withdrawal have been noted in many patients.[12] Our results showed that relapsed patients were prone to experience visual impairment recurrence. A high degree of vigilance is required for patients with MOGAD presenting recurrent ON. Cognitive decline, limb weakness, and autonomic nervous disorders can present in relapses of MOGAD, according to the results of this study.

4.3. Analysis of CSF and MOG-Abs

CSF analysis showed low specificity. The white blood cell and protein content in the CSF increased in a few cases. The MOG-Ab positive rate and titer in the CSF were lower than those in the serum, possibly because the MOG-Abs were derived from peripheral immune cells.[17] Thus, blood serum is the preferred sample type, while CSF antibody testing can provide supplementary information.[18] One study[12] revealed that serum MOG-Ab titers were higher during attacks than during remission and declined at follow-up treatment, indicating that serum titers depended on disease activity and treatment. Our study showed that the serum MOG-Abs remained detectable in most relapsed patients, and the titer was almost the same as that at the initial presentation. The recurrence of MOGAD episodes in many children was associated with persistently high MOG-ab titers.[19] Evidently, rechecking serum MOG-Abs is very important in the assessment of disease recurrence.

4.4. Neuroimaging features

MRI findings of MOGAD displayed a high degree of heterogeneity, and lesions often improved after immunotherapy. Acute lesions were widely distributed. These findings enrich our understanding of the MOGAD neuroimaging spectrum in a Chinese population. We found that intracranial lesions in the cortex/subcortical white matter were the most common, followed by the limbic lobe, brainstem, optic nerve, and cervical spinal cord. One study found cortical lesions in 16.3% of patients.[16] Our findings suggest that the lesion location among Chinese patients with MOGAD is not entirely consistent with that of other reports, possibly owing to racial differences. Cortical gray/juxtacortical white matter lesions on brain MRI could help distinguish MOGAD from AQP4-positive neuromyelitis optica spectrum disorder.[20] Patients with MOGAD can have fluffy brainstem lesions, often located in the pons or adjacent to the fourth ventricle.[21] The corpus callosum, internal capsule, brainstem, and cerebellum can also be affected.[22] Short-segmental lesions were relatively common in the spinal cord. The above-mentioned MRI phenotypes were observed in our study; however, some previous studies described spinal cord H-sign as an indicator of MOGAD diagnosis,[5,23] which was not observed in our study.

The typical manifestations of optic nerve involvement in MOGADON are obvious thickening of the optic nerve with blurred edges and obvious and uniform enhancement.[5] Our results revealed a low positive rate in optic nerve MRI, however, this does not rule out the absence of optic nerve damage. VEP in our study could often detect optic nerve damage (VEP presented delayed latency in P100 wave or amplitude reduction). The degree of amplitude reduction is related to the severity of optic nerve involvement. Hence, the results of VEP have important implications for the location of nerve damage.

4.5. Treatment

Depending on the disease stage, treatment for MOGAD can be divided into acute and maintenance phase therapies. Intravenous MP is the first-line treatment during the acute phase,[1] Second-line therapies, including IVIG and plasmapheresis, are prescribed when the response to intravenous MP is insufficient.[24] Our results showed that MPPT was effective for all patients. Acute attacks in MOGAD appeared to be very responsive to high-dose steroids and plasma exchange,[25] and IVIG may be considered during the refractory cases.

The expert consensus[18] recommends that low-dose prednisone be maintained for 6 months after the initial episode. Most patients in this study received steroid hormones for at least half a year after discharge. However, follow-up showed that 40% had relapsed, often soon after immunotherapy cessation, possibly due to the rapid withdrawal. Some patients with MOGAD might become dependent on steroid hormones. Therefore, the tapering schedule should be slow and can be combined with immunosuppressants.[5] Azathioprine can potentially reduce the recurrence of MOGAD, especially when combined with low-dose steroid hormones.[15,26] The choice and duration of the drugs used to prevent relapse are inconclusive.[7] Relapses often occur during steroid weaning or soon after, suggesting that a longer initial treatment was required.[14] Our study suggested that MOG-Abs, consistently detected during follow-up, could be one of the reasons for relapse. Longitudinal serologic evaluations of MOG-Ab could help predict the disease course and indicate when immunotherapy should be considered.[27]

Determination of whether long-term immunotherapy is necessary for patients with a first MOGAD episode should be based on the lesion location, disease severity, and the MOG-Ab titer.[5] Azathioprine, MMF, rituximab, and particularly IVIG were associated with a reduced relapse frequency,[28] comprising the 4 first-line treatments for recurrence prevention.[24] After the first relapse, maintenance treatment should be initiated to prevent further recurrences and permanent sequelae.[24] In case of further relapse despite maintenance treatment, the consensus group recommends treatment escalation with rituximab[1] or IVIG, followed by their combination, and ultimately adding oral maintenance steroids.[24] Attack-prevention treatments lack class-I data, and empiric maintenance treatment is generally reserved for relapsing cases or patients with severe residual disabilities.[25]

4.6. Prognosis

Our findings revealed that 33.3% of the patients had visible residual neurological deficits, including visual impairment, activity limitations, cognitive impairment, and speech reduction. A previous study reported that 47% of the patients presented with permanent disabilities, such as impaired vision, restricted activity, and bladder, bowel, and erectile dysfunction.[2] Another study indicated that MOGAD resulted in a significant disability in 40% of the patients (mean follow-up, 75.0 ± 46.5 months), with severe visual impairment (36%) and markedly impaired ambulation as the most common long-term sequelae.[12] MOGAD-ON attacks often entail residual symptoms of optic nerve damage. Residual symptoms accumulate gradually after multiple relapses and impaired vision becomes increasingly severe. Severe vision loss is associated with more recurrences.[29] Recurrence of diseased eyes is an independent risk factor for poor visual prognosis.[9] Thus, it is essential to maximize visual recovery and minimize recurrences of OA.[30] Future research is required to determine the optimal long-term disease management strategy.[4]

4.7. Limitations

Only a few cases were included in this study, reflecting the clinical phenotypes and prognosis of patients (mainly adults) with MOGAD in southern China. However, our results yield valuable information for disease management. Large, prospective studies are required to validate and expand on our findings.

5. Conclusion

Our findings enrich the understanding of the clinical phenotypes and neuroimaging spectrum of MOGAD in a Chinese population (especially for adults). The long-term recurrence rate was high. Serum MOG-Abs were consistently detected, and the titers remained stable through recurrence, suggesting that MOGAD recurrence may be associated with inappropriate maintenance immunotherapy. Residual neurological deficits and other sequelae of MOGAD should not be ignored. Our findings provide a basis for larger, multicenter studies to better understand the disease and its management.

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