Clinical features of demyelinating optic neuritis with seropositive myelin oligodendrocyte glycoprotein antibody in Chinese patients

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ABSTRACT

Background/aims To investigate the clinical features of demyelinating optic neuritis (ON) in Chinese patients with seropositive myelin oligodendrocyte glycoprotein antibody (MOG-Ab) and compare them with Aquaporin-4 antibody (AQP4-Ab) ON.

Methods In this retrospective observational study, sera from patients with demyelinating ON were tested for MOG-Ab and AQP4-Ab with a cell-based assay. Clinical characteristics were compared between MOG-Ab-related ON (MOG-ON) and AQP4-Ab-related ON (AQP4-ON), including visual performances, serum autoantibodies and features on MRI.

Results A total of 109 affected eyes from 65 patients with demyelinating ON (20 MOG-ON and 45 AQP4-ON) were included. The onset age of MOG-ON was younger than AQP4-ON (MOG-ON: 20.2±17.4 years old, AQP4-ON: 35.6±15.7 years old, P=0.001). Onset severity was not different between these two groups (P=0.112), but patients with MOG-ON showed better visual outcomes at onset (P=0.004). Half of the MOG-ON had a relapsing disease course. Nineteen per cent of patients with AQP4-ON were coexisting autoimmune disorders, but there were no coexisting autoimmune disorders among patients with MOG-ON. Optic nerve head swelling was more prevalent in patients with MOG-ON (P=0.01). Retrobulbar segment involvement of the optic nerve were more common in patients with MOG-ON according to our MRI findings (P=0.01). Patients with MOG-ON showed longitudinally extensive lesion in 30% and chiasm and optic tract involvement in 5%.

Conclusions MOG-ON is not rare in Chinese demyelinating patients. It underwent a severe vision loss at onset but had relatively better visual recovery than patients with AQP4-ON. MOG-ON might have an unique pathogenesis different from AQP4-ON.

INTRODUCTION

Optic neuritis (ON) is one of the most common types of acute optic neuropathy in young individuals, especially under age of 45 years old. It has been associated with demyelinating diseases.1 Many studies have demonstrated that the pathogenesis of ON could be related to specific autoantibodies that damage the integrity of myelin surrounding the optic nerves, resulting in severe visual impairment.2 Demyelinating ON is the main manifestation of central nervous system (CNS) inflammatory demyelinating diseases (IDDs) in ophthalmology. Neuro-mytelitis optica (NMO) is the more common CNSIDD in Chinese population.3 ON was the initial feature in approximately 50% of patients with NMO.4 Aquaporin-4 antibody (AQP4-Ab) has been known as the most important biomarker for NMO.5 However, about 10%–20% of patients with NMO were serological AQP4-Ab negative.6 Recently, myelin-oligodendrocyte glycoprotein antibody (MOG-Ab) was discovered in some AQP4-Ab-negative NMO patients, and a better prognosis was reported in this subset of patients.7–10 In contrast, a multicentre study conducted by the Neuromyelitis Optica Study Group (NEMOS) reported that 64% MOG-IgG-positive patients initially presented with isolated ON and showed predominantly a relapsing and frequently aggravated disease course.11 The study of Hacohen et al12 found that 35% of patients with childhood acquired demyelinating syndrome (ADS) were MOG-Ab-positive and 52% of MOG-Ab-positive patients were ON. One study of Chinese patients with CNS IDD found that ON was the most frequent clinical presentation at onset (75.0%) or during the whole disease course (83.3%) in MOG-Ab-associated IDDs.13 Some previous studies involving patients with NMO spectrum disorders (NOMSD)14 observed retinal neuroaxonal damage in MOG-Ab-positive patients, with or without ON.

As a different biomarker, MOG-Ab might predict a diseases course different from AQP4-Ab. It might play an essential role in the diagnosis and management of patients with ON. Few previous studies15 16 have focused on the MOG-Ab serostatus in patients with ON, and those were limited by a relatively small MOG-ON sample size.

The current study aimed to present the clinical characteristics of MOG-ON and compared with the features of AQP4-ON in Chinese patients.

MATERIALS AND METHODS

This was a retrospective observational study on patients diagnosed with ON in the Neuro-ophthalmology Department of the Chinese People’s Liberation Army General Hospital (PLAGH), between 1 May 2016 and 1 October 2016. The study protocol was approved by the institutional review board at the Chinese PLAGH and adhered to the tenets of the Declaration of Helsinki.

Diagnostic criteria

The diagnosis of demyelinating ON was based on the criteria established by the Optic Neuritis
Treatment Trial (ONTT) Group: (1) acute vision loss involving one or both eyes with or without eye pain; (2) presence of a relative afferent papillary defect or presence of visual evoked potential abnormalities; and (3) abnormal visual field consistent with optic neuritis. 

Subjects who fulfilled any of the following criteria were excluded: (1) any secondary or other types of optic neuropathy, for example, compressive, vascular, toxic, metabolic, infiltrative or hereditary optic neuropathy; (2) corneal opacity, dense cataract and glaucoma, vitreous or retinal diseases; or (3) no positive response to serological tests of AQP4-Ab or MOG-Ab with cell-based assay.

Laboratory examinations

Results of blood tests on all study subjects were collected, including erythrocyte sedimentation rate and C reaction protein analyses, total antinuclear antibodies (ANAs) titre, Sjögren’s syndrome A (SSA)/B (SSB), proliferating-cell nuclear antigen, antineutrophil cytoplasmic antibodies, rheumatoid factor and major histocompatibility complex-B27 (HLA-B27). The thyroperoxidase antibody and thyroglobulin antibody was tested by chemiluminescence immunoassay. Additionally, results of cerebrospinal fluid (CSF) tests were also collected, including cell counts, levels of total protein, glucose and chloride, as well as oligoclonal band (OCB) examination. The criteria of elevation in CSF tests were defined as: white cell count elevated: white cell count >10/μL; protein elevated: protein >400 mg/L; IgG level elevated: IgG level >3.4 mg/dL.

AQP4-Ab and MOG-Ab assays

Patients with demyelinating ON underwent serum tests for anti-AQP4-IgG and anti-MOG-IgG with cell-based assay (CBA). The procedure of AQP4 antibody detection in living cells was described previously. In terms of MOG antibodies testing, live HEK-293 cells were transiently transfected with a plasmid containing full-length human MOG cDNA before it exposed to the patients’ diluted serum. Goat anti-human IgG labelled with Alexa488 was used as a secondary antibody. Two independent and masked evaluators identified the scores as positive or negative. The serums were titrated in 1:10 dilutions afterwards to determine the highest dilution level where scores remain positive.

Ophthalmic examinations and therapy

All subjects received a series of ophthalmic examinations, including the relative afferent papillary defect test, the slit-lamp biomicroscopy examination, intraocular pressure document and the fundus evaluation. Best-corrected logarithm of the minimum angle of resolution (LogMAR) visual acuity (VA) was performed on the standard table at 5 m distance. For those subjects who were unable to read letters at 1 m distance, they would be further examined by finger counts, hand movements or perceiving light. The retinal thickness was assessed by the high-definition spectral-domain optical coherence tomography (Carl Zeiss Meditec, Dublin, Ohio, USA). The orbit, brain and spinal MRI were also preformed and evaluated according to Paty criteria using MRI-3.0T (TW1WSPEED HDXT, Georgia, USA) with post-contrast T1-weighted conventional spin-echo (repetition time (TR)=680 ms; echo time (TE)=14 ms, field of view (FOV)=24, slice thickness=3.0, interleaved) at 5 min after the intravenous administration of 0.1 mmol/kg gadopentetate dimeglumine. All patients were treated with intravenous methylprednisolone and oral steroids therapy in acute phase.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of demographic characters between the patients with MOG-ON and AQP4-ON</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients (N)</strong></td>
<td>MOG-ON</td>
</tr>
<tr>
<td>20</td>
<td>45</td>
</tr>
<tr>
<td><strong>Number of affected eyes (N, %)</strong></td>
<td>34/40, 68</td>
</tr>
<tr>
<td>Ethnicity (Han Chinese) (N, %)</td>
<td>20/20, 100</td>
</tr>
<tr>
<td><strong>Sex (female, %)</strong></td>
<td>14/20, 70</td>
</tr>
<tr>
<td><strong>Age (years, mean±SD)</strong></td>
<td></td>
</tr>
<tr>
<td>At first attack</td>
<td>20.2 (17.4)</td>
</tr>
<tr>
<td>At sampling</td>
<td>22.7 (15.9)</td>
</tr>
<tr>
<td>Age at first attack &lt;18 years (N, %)</td>
<td>13/20, 65</td>
</tr>
<tr>
<td>Observation time (months, mean±SD)</td>
<td>29.0±32.5</td>
</tr>
</tbody>
</table>

*Pearson χ² test. †Fisher’s exact test. ‡Independent t-test.

AQP4, aquaporin-4; AQP4-ON, AQP4 antibody-associated ON; MOG, myelin oligodendrocyte glycoprotein; MOG-ON, MOG antibody-associated ON; ON, optic neuritis.

Statistical analysis

Differences of continuous data were compared by independent t-test (normal distribution) or Mann-Whitney U test (non-normal distribution). Normality of the data was tested using Shapiro-Wilk test. Categorical data were compared using Pearson χ² test or Fisher’s test. A two-tailed P value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (V.17.0).

RESULTS

Demographic manifestations

A total of 65 patients (109 affected eyes) were recruited in this study, consisting of 20 patients (30.8%) with serological positive MOG antibodies (MOG-ON) and 45 patients (69.2%) with serological positive AQP4 antibodies (AQP4-ON). The patients with MOG-ON had a younger age of disease onset at 20.2±17.4 years old (range: 5–63 years old) compared with the AQP4-ON group with 51.0±65.9 months, but this difference was not statistically significant (P=0.100). The interval time from the first to the second attack was 28.6±30.1 months (range: 5–96 months) in the MOG-ON group, whereas 31.1±35.3 months (range: 3–132 months) in the AQP4-ON group (P=0.842). There was no significant difference
in the number of eyes with severe visual loss (defined as best-corrected VA (BCVA) <0.1) at Nadir between the two groups. Interestingly, the visual acuity outcomes of patients with MOG-ON were significantly better than patients with AQP4-ON from the Nadir episode, representing fewer cases suffered from severe visual loss (BCVA <0.1) at the latest follow-up in the MOG-ON group (MOG-ON: 20%, AQP4-ON: 46.7%, P=0.004).

Comparison of laboratory findings, according to antibody status

Comparison of laboratory findings between the patients with MOG-ON and AQP4-ON was summarised in Table 3. There were 42.2% of patients with AQP4-ON presented coexisting autoimmune disorders, including seropositivity of anti-SSA/SSB antibody, anti-ANA, HLA-B27 antibodies and thyroid-related autoantibodies, but no coexisting autoimmune disorders in patients with MOG-ON (P=0.001). In terms of the CSF tests, elevated protein levels occurred in 6.7% of patients with AQP4-ON, but not in patients with MOG-ON (P=0.547). White cell counts were raised in 11.1% of patients with AQP4-ON, and in 5% of patients with MOG-ON (P=0.748). There was one patient with MOG-ON responded positive for OCBs, whereas none in AQP4-ON samples (P=0.308).

Comparison of MRI manifestation according to antibody status

All of the involved optic nerves were revealed for T2 hyperintensity (with or without enhancement) through MRI. An example of abnormal findings on the MRI of optic nerve in a MOG-ON and a AQP4-ON patients were shown in figure 1. Table 4 summarised the comparison of MRI manifestations between the MOG-ON and AQP4-ON groups. Retrobulbar segment involvement on the optic nerve was found in majority of patients with MOG-ON (MOG-ON: 80%, AQP4-ON: 20%, P<0.001), whereas canalicular portion of optic nerve was involved more in patients with AQP4-ON (MOG-ON: 30%, AQP4-ON: 57.8%, P=0.039). In addition, the lesions on patients with AQP4-ON showed a higher portion of longitudinally extensive optic nerve lesion (57.8%) than MOG-ON (30%) (P=0.039). Besides, 15% of patients with AQP4-ON had optic chiasma and 5% had optic tract involvement.

DISCUSSION

MOG antibodies have been reported to be associated with a variety of demyelinating diseases, such as NMOSD,7 ON and acute disseminated encephalomyelitis (ADEM).20 MOG has been considered as a conformational dependent antibodies for ADEM.21 About one-third of patients with childhood ADS were reported with serological-positive MOG antibodies, such as clinically isolated syndrome, multiple sclerosis and ADEM.22 In addition, about 17.8% of MOG-IgG-positive patients were reported as ADEM with ON or long extensive transverse myelitis, while 12.7% of them presented as NMO, 49.2% presented as ON. By contrast, among AQP4-IgG-positive patients, there were 47.1% presented as NMO, 9.5% presented as ON, but none presented as ADEM.23 Furthermore, evidence showed that the severity of disease in ADEM was associated with the titre of MOG-IgG.24 MOG antibodies could play an important role in ADEM clinically. Nevertheless, the patients recruited in the study were not having enough evidence to diagnosed as ADEM or NMO, conversion of the clinical subtypes should be confirmed in the further longitudinal study.

The differences in antibody assays often lead to non-specific results or false positives. Western blot and ELISA are traditionally used to detect MOG antibodies, but these assays may lead to conflicting results. The CBA is a universal method for MOG-Ab and AQP4-Ab detection and recommended by the International Panel for NMO Diagnosis.25 Twenty MOG-Ab-positive patients and 43 AQP4-Ab-positive patients were screened out by the cell-based assay in this study.

The patients with MOG-ON had younger disease onset with an average of 20.2±17.4 years old than patients with AQP4-ON with 35.6±15.7 years old in this cohort (P=0.001). This finding was consistent with previous reports that compared between MOG-ON (32.29±17.1 years old) and AQP4-ON (44.86±14.8 years old),8 MOG-ON (31 years old) and AQP4-ON (38 years old),10 MOG-ON (20±14 years old) and AQP4-ON (23±14 years old).
Figure 1  Optic nerve abnormalities detected by MRI in patients with MOG-ON and AQP4-ON (A and B) coronal T2-weighted images from a 10-year-old girl with seropositive MOG-Ab relapsing ON. (A) Lesions in bilateral retrobulbar segment of the optic nerve on the first attack. (B) Lesions in bilateral retrobulbar segment of the optic nerve on the second attack, 1 year after the first attack. (C–F) Images from a 5-year-old girl with seropositive MOG-Ab bilateral ON showing longitudinally extensive bilateral optic nerve lesion extending from the chiasm. (C) Axial T2-weighted Image. (D) T1 postcontrast images. (E) Coronal T2-weighted Image. (F) T1 postcontrast image. (G and H) Images from a 41-year-old woman with seropositive AQP4-Ab ON. (G) Coronal T2-weighted image showing extensive T2 high signal in the right posterior portion of the optic nerve. (H) Sagittal Gd enhancement T1-weighted image, showing lesion in the right posterior portion of the optic nerve with marked postcontrast enhancement. (I and J) Images from a 51-year-old man with seropositive AQP4-Ab ON. (I) Axial T2-weighted image, showing extensive T2 high signal in the right posterior portion of the optic nerve. (J) Axial Gd enhancement T1-weighted image showing lesion in the right posterior portion of the optic nerve with marked postcontrast enhancement. AQP4-ON, aquaporin-4 antibody-associated ON; MOG-ON, myelin oligodendrocyte glycoprotein antibody-associated ON; ON, optic neuritis.

Table 4  Comparison of orbital MRI findings in the patients with MOG-ON and AQP4-ON

<table>
<thead>
<tr>
<th></th>
<th>MOG-ON</th>
<th>AQP4-ON</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, (n)</td>
<td>20</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Orbital MRI lesion, n/total (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 lesion</td>
<td>20/20, 100</td>
<td>45/45, 100</td>
<td>0.570</td>
</tr>
<tr>
<td>Post-enhancement</td>
<td>16/20, 80</td>
<td>40/45, 88.9</td>
<td>0.197</td>
</tr>
<tr>
<td>Radiological bilateral ON</td>
<td>14/20, 70</td>
<td>30/45, 66.7</td>
<td>0.791</td>
</tr>
<tr>
<td>Optic nerve head swelling</td>
<td>16/20, 80</td>
<td>9/45, 20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retrobulbar</td>
<td>16/20, 80</td>
<td>9/45, 20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Canalicular</td>
<td>6/20, 30</td>
<td>26/45, 57.8</td>
<td>0.039</td>
</tr>
<tr>
<td>Intracranial</td>
<td>3/20, 15</td>
<td>16/45, 35.6</td>
<td>0.093</td>
</tr>
<tr>
<td>Chiasmal involvement</td>
<td>3/20, 15</td>
<td>10/45, 22.2</td>
<td>0.737</td>
</tr>
<tr>
<td>Optic tract involvement</td>
<td>1/20, 5</td>
<td>3/45, 6.7</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Longitudinally extensive optic nerve lesion</td>
<td>6/20, 30</td>
<td>26/45, 57.8</td>
<td>0.039</td>
</tr>
<tr>
<td>Brain MRI lesion, n</td>
<td>2/5</td>
<td>8/25</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Spinal MRI lesion, n</td>
<td>0/8</td>
<td>17/32</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Longitudinally extensive optic nerve lesion: the lesion involved more than 1/2 segments of the whole optic nerve.

*Pearson χ² test.

AQP4-ON, aquaporin-4 antibody-associated ON; MOG-ON, myelin oligodendrocyte glycoprotein antibody-associated ON; ON, optic neuritis.

More than half (65%) of our patients with MOG-ON had a juvenile (<18 years) disease onset, which was more than those reported by previous study showing about 12.5%, 9 50% 10 or 16.7% 11 of MOG-Ab-positive patients with demyelinating diseases began during juvenile period. The age at MOG-ON onset ranged from 5 years to 63 years, and the age at AQP4-ON onset ranged from 8 years to 72 years. Both of MOG-ON and AQP4-ON could occur in children or in the elderly. This result was similar to previous reports. 9 12

More than 90% of patients with AQP4-ON were female indicating a strong female predominance in patients with AQP4-ON. Similar female/male ratio was also observed in AQP4-Ab-positive demyelinating disease in the other studies. 9 In contrast, patients with MOG-ON had a less female preponderance, 70% of MOG-ON patients were female; nevertheless, females still accounted for the majority among patients with MOG-ON in this study. However, the sex ratios were variable in the previous reports, females accounted for between 37.5% and 75%. 8 9 10 26

Bilateral ON and optic disc swelling were commonly observed in our Chinese MOG-ON cohort, which was corresponding with those patients with MOG-ON in various ethnic groups. 26 However, previous reports indicated that most of the MOG-Ab-positive patients presented as monophasic disease or had less relapsing rate, 8 9 which was different from the current study demonstrating both patients with MOG-ON and AQP4-ON had high recurrent episodes. However, in some other studies, patients with MOG-ON were frequently associated with a recurrent disease course. 14 This study indicated that Chinese patients with MOG-ON might also have a high tendency to relapse, so that long-term immunotherapy should be considered in relapsing patients with MOG-ON.

Most of the patients with MOG-ON in this study were suffered from severe vision loss at the first attack but had relatively good visual recovery by comparing with patients with AQP4-ON. The ONTT studies reported 50% of patients with idiopathic demyelinating ON could have visual recovery of 20/20 and 68% had 20/40 or better vision after 1 year. 22 27 In our previous
study, the BCVA in AQP4-Ab-negative ON eyes was better than AQP4-Ab-positive ON eyes. In NEMOS of Caucasian descent, the patients’ VA was less impaired in the MOG-ON subgroup than in the AQP4-ON subgroup after more than 3 months follow-up, but the difference was not significant. The results from our Chinese cohort showed that the onset episode severity of patients with MOG-ON was similar to AQP4-ON ones but had a better visual recovery for the former group of patients.

Coexisting autoimmune disorders were presenting in more than one-fourth (19/73) of our patients with AQP4-ON. This phenomenon was also observed in AQP4-Ab-positive NMO. By contrast, coexisting autoimmune disorders were absent in all of the MOG-ON patients in our Chinese cohort. It was in line with previous reports that suggested patients with AQP4-ON were involved in the anterior optic nerve segment, whereas patients with MOG-ON involved the posterior optic nerve segment. Nevertheless, there were 3/20 (15%) of lesion on patients with MOG-ON involved optic chiasm, and 1/20 (5%) of the encountered lesions involved optic tract in the current study, which indicated that MRI manifestation of MOG-ON could be longitudinally extensive and affect the entire visual pathway.

Some limitations still exist in the current study. First, all of the recruited subjects were collected from the single neuro-ophthalmology centre in the northern China instead of a multicentre study. Second, because the patients presented ocular symptoms and visited ophthalmology clinic first, some MOG-Ab-positive patients with non-ocular demyelinating disorders could not be investigated. Larger investigations cooperation with neurology department and other institutes should be conducted in the further study. Third, longitudinal study should also be necessary in Chinese patients with MOG-ON to investigate the conversion rate of NMO-SD or ADEM.

In summary, the clinical features of MOG-ON in Chinese demyelinating ON were not mild like previous reports. Most of patients with MOG-ON underwent a severe vision loss at onset and had a high relapsing tendency. MOG-ON had some distinct clinical features with AQP4-ON, such as a high rate of optic disc involvement, less overlapping pathogenesis with autoimmune disorders and also a better visual recovery. We believed that MOG-ON might have its unique pathogenesis, which was different from AQP4-ON. MOG-Ab should be tested in patients with demyelinating ON as a serological clinical biomarker in clinical management.

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Contributors YZ and ST: study design, manuscript draft and revision, data collection and statistical analysis. TCYC: study design and manuscript revision. QX: study design and manuscript revision. IZ, DT and HF: study design and data collection. SW: study design, correspondence and manuscript revision.

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Clinical science


