Neurochemistry International 130 (2019) 104319

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

Clinical spectrum of inflammatory central nervous system demyelinating disorders associated with antibodies against myelin oligodendrocyte glycoprotein

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A B S T R A C T

Immunoglobulin G (IgG) antibodies against myelin oligodendrocyte glycoprotein (MOG) are detected in the serum of some patients with demyelinating diseases. These patients are known to show repeated clinical episodes of inflammatory demyelinating attacks in the central nervous system. Although the associated pathogenicity and mechanism of inflammatory demyelination remains inconclusive, it is known that patients with MOG-IgG antibodies have a different clinical spectrum from those with other demyelinating diseases, such as multiple sclerosis. Based on our database of 85 MOG-IgG positive (+) cases, the most frequently associated clinical episodes were isolated optic neuritis (67.5%), encephalitis (26.5%), and myelitis (19.3%). Optic neuritis in MOG-IgG (+) disease usually involves the long segment of optic nerves and sometimes happens bilaterally, but visual acuity usually recovers with proper treatment in the acute phase. Brain and brainstem lesions usually present vague and focal appearances with irregular margins, typically in subcortical or brainstem regions, but occasionally in the cortex or corpus callosum. Due to these characteristics, MOG-IgG (+) cases with brain or brainstem lesions are sometimes diagnosed with acute disseminated encephalomyelitis, meningitis, or symptomatic epilepsy. The myelitis in MOG-IgG (+) typically shows longitudinally extensive lesions as seen in neuromyelitis optica spectrum disorders. Acute treatment to reduce attack-related disability is recommended in MOG-IgG (+) disease, and long-term immunosuppression may be considered in patients with a high frequency of relapses and/or high risk of neurological disability.

1. Introduction

Patients with inflammatory idiopathic central nervous system (CNS) disorders usually show relapsing–remitting clinical courses that probably reflect underlying immune-mediated mechanisms. Indeed, a subgroup of patients are known to present predominantly with optic neuritis (ON) and myelitis, without typical MRI findings of multiple sclerosis (MS), and were diagnosed with neuromyelitis optica spectrum disorders (NMOSD). In 2005, serum immunoglobulin G (IgG) antibodies against aquaporin-4 (AQP4-IgG) were shown to be present in most patients with NMO (Lennon et al., 2005). Since then, patients with serum AQP4-IgG and repeat episodes of ON and myelitis have been diagnosed with NMO spectrum disorders (NMOSD), which is considered a different disease entity to MS (Wingerchuk et al., 2006, 2015). Even at the microscopic level, these diseases show very different background pathologies; the primarily damaged glial cells in MS and in NMOSD are oligodendrocytes and astrocytes, respectively (Barnett and Prineas, 2004; Jacob et al., 2013).

Recently, serum IgG antibodies against myelin oligodendrocyte glycoprotein antibody (MOG) were reported to be present in some patients with atypical MS, seronegative NMO, and isolated ON (Mader et al., 2011; Kitley et al., 2012). Because the clinical spectrums (e.g., onset age, clinical episodes, and MRI appearance) of patients with MOG-IgG in their serum vary from those of patients with MS and NMOSD, potential differences in pathogenesis are now being discussed (Reindl et al., 2017). Although there are no conclusive data on the pathogenesis, we do know that patients with serum MOG-IgG differ clinically from those without it, not least in the types of clinical episode and in the appearance of MRI lesions (Wingerchuk et al., 2015). Today, checking for serum MOG-IgG positivity as a diagnostic marker is considered invaluable when determining therapy (Thompson et al., 2018), yet MOG-IgG levels are not widely measured. This limits our ability to understand the full clinical spectrum of MOG-IgG (+) disease.

In this report, we reviewed evidence about the clinical spectrum of MOG-IgG (+) disease with the data of 85 patients with MOG-IgG (+) disease treated at our facility. Our aim was to provide a reliable description of what is currently known about the identification, clinical spectrum, and treatment of this pathology.

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https://doi.org/10.1016/j.neuint.2018.10.016
Received 13 August 2018; Received in revised form 8 October 2018; Accepted 17 October 2018
Available online 23 October 2018

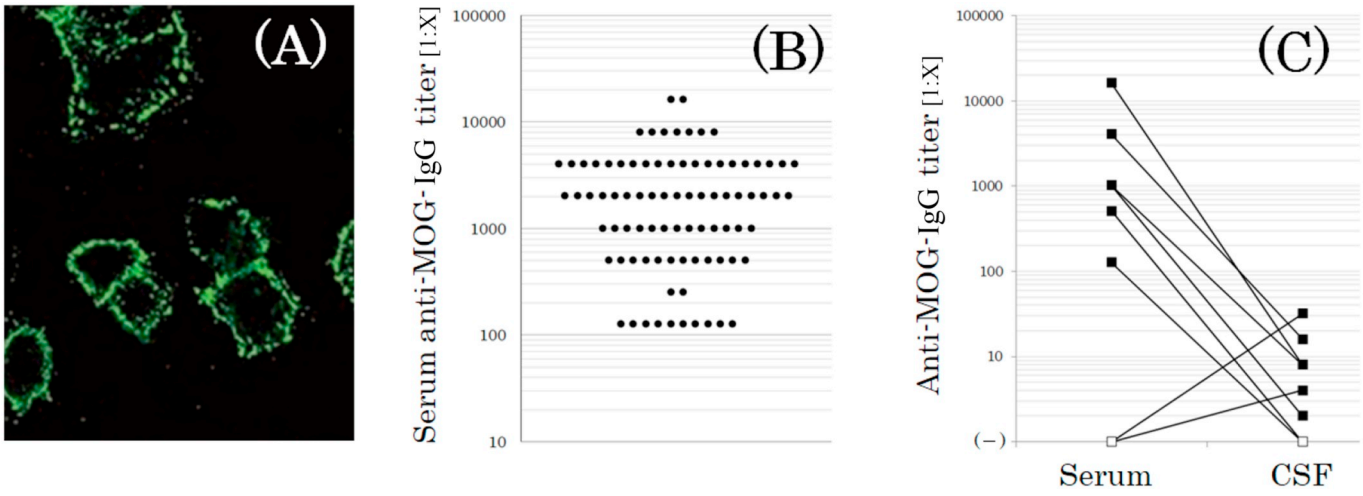

Fig. 1. Measurement of MOG-IgG titers in the serum and CSF. (A) A representative image of an immunofluorescent assay by the cell-based assay method. Live cells with MOG protein forcedly expressed on their surface are combined with labeled MOG-IgG from patients. (B) The serum MOG-IgG titers in the acute phase of clinical episodes for our cohort of 85 patients with MOG-IgG (+) disease. Note that the vertical axis is logarithmically transformed. (C) Comparisons of MOG-IgG titers in the serum and CSF of six MOG-IgG (+) patients, together with those in two patients who were positive for MOG-IgG in the CSF, but negative in the serum. Abbreviations: MOG-IgG, anti-myelin oligodendrocyte glycoprotein IgG; CSF, cerebrospinal fluid.

Table 1
Comparisons of clinical information among MS-related disorders.

	MOG-IgG (+)	AQP4-IgG (+)	MS	p
Number of patients	85	110	209	–
Male: Female	35: 50	5: 105	53: 156	< 0.0001
Onset age	35.7 ± 19.8	42.6 ± 14.0	29.9 ± 9.8	< 0.0001
Duration [years]	6 (3–10)	8 (3–15)	9 (4–14)	0.0705
latest EDSS	0 (0–1.0)	4.5 (3.0–6.0)	2.0 (1.0–4.0)	< 0.0001
MSSS	1.10 ± 1.98	6.09 ± 2.74	3.63 ± 2.72	< 0.0001
Total relapse [times/each patient]	0 (0–1)	2 (1–5)	2 (1–5)	< 0.0001
Annual relapse rate	0.07 ± 0.17	0.43 ± 0.49	0.43 ± 0.41	< 0.0001
Percentages of each impaired lesion among total clinical episodes				
Total episodes [times]	166	313	366	–
Optic neuritis	67.5%	32.6%	22.4%	< 0.0001
(Bilateral optic neuritis)	(18.7%)	(1.6%)	(1.6%)	(< 0.0001)
Myelitis	19.3%	64.5%	45.1%	< 0.0001
Brain & brainstem	26.5%	16.9%	42.1%	< 0.0001

Data shown are mean ± standard deviation, number, percentage, or median and the range (first and third quartiles). P-values are for analysis of variance (normal data), Kruskal–Wallis test (non-normal data), and chi-squared test (frequency data). Note that the summed percentages of clinical subtypes in the lower table surpass 100% because there may be overlap in each clinical episode. Abbreviations: AQP4-IgG, anti-aquaporin-4 IgG; EDSS, expanded disability status scale; MOG-IgG, anti-myelin oligodendrocyte glycoprotein IgG; MS, multiple sclerosis, MSSS, multiple sclerosis severity score.

2. Measurement of MOG-IgG

2.1. Cell-based assay method for MOG-IgG

MOG-IgG autoantibodies were originally tested by linear epitope assays, such as western blotting or enzyme-linked immunosorbent assay. However, those failed to provide consistent results, and recent studies have shown that the conformational epitope is required to detect clinically significant MOG-IgG levels (Ramanathan et al., 2016). Therefore, MOG-IgG testing is done by cell-based assay (CBA), which can detect the extracellular epitope in its natural conformation. In our center, these samples were analyzed for the presence of MOG-IgG using a CBA with live stably transfected full-length human MOG-expressing HEK293 cells and a goat anti-human Fc-specific IgG cross-adsorbed secondary antibody (Pierce Biotechnology) to reduce the risk of light chain cross-reactivity from other immunoglobulin subclasses. The samples were tested for MOG antibodies at least twice at dilution of 1:128. The antibody titers were calculated semi-quantitatively using consecutive two-fold endpoint dilutions. All MOG-IgG positive serum samples were also confirmed at dilution of 1:20 using a mouse anti-human IgG1 Fc secondary antibody (Thermo Fisher Scientific).

In CBA, antibody binding is analyzed by microscopy (Fig. 1A) or flow cytometry based on the fact that the antigen is expressed on the cell surface of mammalian cells (Reindl et al., 2017; Ramanathan et al., 2016). The method using live cells is called “live CBA” and is believed to have improved sensitivity and specificity compared with CBA using fixed cells. Presently, there are two major live CBAs for MOG-IgG testing, the so-called “high-titer” cut-off method and the MOG-IgG1 detecting method (Reindl et al., 2017). The high-titer cut-off method typically detects MOG-IgG using diluted serum to avoid non-specific findings (Di Pauli et al., 2011; Reindl et al., 2017). Despite its widespread use, this method tends to have produced inconsistent results in different studies because the secondary antibody conditions have not been specified. By contrast, the MOG-IgG1 method detects the IgG1 subclass of MOG-IgG to avoid non-specific findings (Reindl et al., 2017; Waters et al., 2015). This assay is more specific than the high-titer method, but fails to identify patients with IgG2, IgG3, or IgG4 subclasses. At this time, it is unclear which method is optimal for use in routine MOG-IgG testing, so a multicenter comparison and standardization of the assays is needed in future research.

2.2. MOG-IgG titers in our cohort of 85 MOG-IgG (+) cases

The distribution of the serum MOG-IgG titers measured in 85 MOG-IgG (+) cases followed at Tohoku University Hospital are shown in Fig. 1B. Among these, six also had their MOG-IgG titers measured in the cerebrospinal fluid (CSF), and the paired titers are shown in Fig. 1C. In most of these patients, serum titers were more than 100 times higher than the CSF titers; however, in two patients, MOG-IgG was detected only in the CSF and not in the serum. The two patients with isolated CSF titers were not included in the following evaluations, but their paired titers have been superimposed in Fig. 1C to allow comparison with the

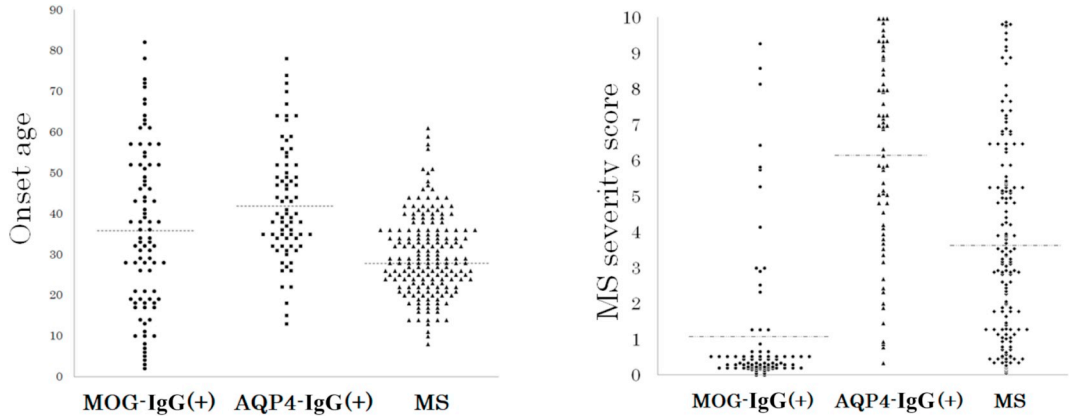

Fig. 2. Comparisons of onset age and clinical severity among the CNS diseases. MS had the youngest age distribution while MOG-IgG (+) had the widest age distribution. The MS severity score was most severe for AQP4-IgG (+) and least severe for MOG-IgG (+). Broken lines show the means for each disease. Abbreviations: AQP4-IgG, anti-aquaporin-4 IgG; CNS, central nervous system; MOG-IgG, anti-myelin oligodendrocyte glycoprotein IgG; MS, multiple sclerosis.

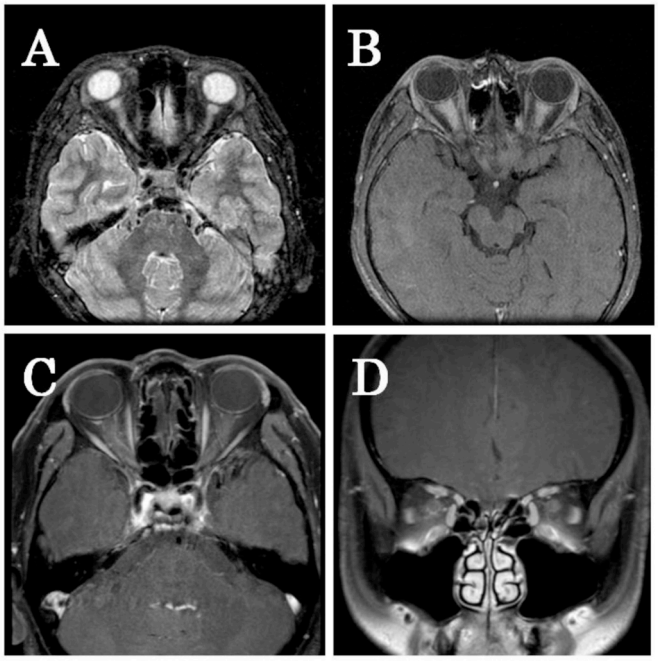

Fig. 3. Representative MRI images of acute optic neuritis in MOG-IgG (+) disease. (A, B) Short-tau inversion recovery and fat-suppressed contrasted T1-weighted MRI images in a 17-year-old male with serum MOG-IgG. The optic nerves on both sides are swollen with high-signal in the surrounding intra-orbital fat tissues, which is suggestive of inflammation. (C, D) Axial and coronal views of fat-suppressed contrasted T1-weighted MRI images in a 72-year-old male initially diagnosed with optic perineuritis. Contrast-enhancement can be seen around the right optic nerve.

other results. Thus, although it is quite rare and titers tend to be low (i.e. < 1:100), it is useful to know that some patients have MOG-IgG detected only in the CSF.

Notably, serum MOG-IgG titers were measured by the live CBA method in all patients with serum AQP4-IgG at our hospital (n = 110), yet MOG-IgG was not detected in any cases. This suggests that AQP4-IgG and MOG-IgG identifies different subgroups of patients that may share some clinical phenotypes.

3. General information of MOG-IgG (+) patients

3.1. Clinical spectrum

The clinical and demographic data for the 85 patients with serum MOG-IgG followed at Tohoku University Hospital are listed in Table 1. Their characteristics are compared against those in cases of serum AQP4-IgG (+) and MS. The female predominance was greatest in the order AQP4-IgG (+), MOG-IgG (+), and MS. As shown in Fig. 2A, patients with MS developed the disease at the youngest age, while patients with MOG-IgG (+) had the widest age distributions, ranging from infancy to old age. As shown in Fig. 2B, neurological prognosis, assessed by the MS severity score (MSSS), disease duration, and the expanded disability status scale (EDSS), was most severe in the AQP4-IgG (+) group and was least severe in the MOG-IgG (+) group. Annual relapse rates were similar in the AQP4-IgG (+) and MS groups, but were much lower in the MOG-IgG (+) group.

The most frequent clinical episodes for each disease type were as follows. In the MOG-IgG (+) group, it was isolated acute ON without other CNS lesions. In the AQP4-IgG (+) group, it was acute myelitis. In the MS group, episode of acute myelitis and brain or brainstem lesions occurred at comparable frequencies, but acute ON was less frequent. Of note, the frequency of simultaneous bilateral ON was significantly higher in the MOG-IgG (+) group than in either the AQP4-IgG (+) or the MS groups. In all three diseases, the clinical episodes could change over time in a given patient. For example, a patient with serum MOG-IgG who initially presented with unilateral ON may have a relapse with cerebral lesions several years after the initial episode of ON.

3.2. Clinical significance of serum titers

We also evaluated whether the serum MOG-IgG titers in the acute phases of clinical episodes correlated with other clinical information. However, no significant correlations ($p \geq 0.10$) were observed between the serum MOG-IgG titer and either the sex, onset age, CSF MOG-IgG titer, clinical episode type (i.e., ON, myelitis, brain/brainstem lesions), relapse rates, or clinical severity. Although the acute serum MOG-IgG titer did not correlate significantly with these variables, this does not mean it has no clinical meaning or that it is a mere epiphenomenon. Indeed, when we measured serum AQP4-IgG titers in 110 patients with NMOSD (where pathogenicity is established), no significant correlations were shown with either relapse rate, clinical severity, clinical episode types, CNS lesion volume, or CNS lesion length.

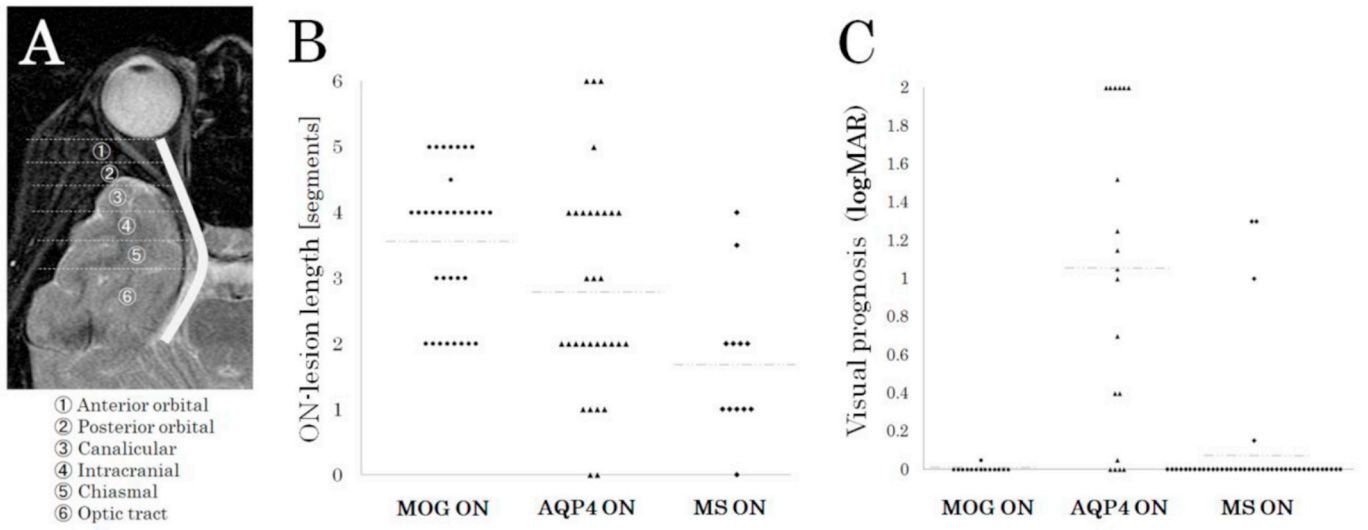

Fig. 4. Comparisons of ON lesion length and visual prognosis among the diseases. (A) The longitudinal length of an ON lesion was represented by the number of involved optic nerve segments, as shown. (B) Lesion length was much longer in MOG-IgG (+) ON and AQP4-IgG (+) ON than in MS-related ON. (C) Visual prognosis 5 years after onset was much better in MOG-IgG (+) ON and MS-related ON than in AQP4-IgG (+) ON. The vertical axis shows the corrected visual acuity, measured with a logMAR scale between 0.0 (best) and 2.0 (worst). The broken lines indicate the means for each subgroup. Abbreviations: AQP4 ON, anti-aquaporin-4 IgG positive optic neuritis; MOG ON, anti-myelin oligodendrocyte glycoprotein IgG positive optic neuritis; MS-ON, optic neuritis related to multiple sclerosis.

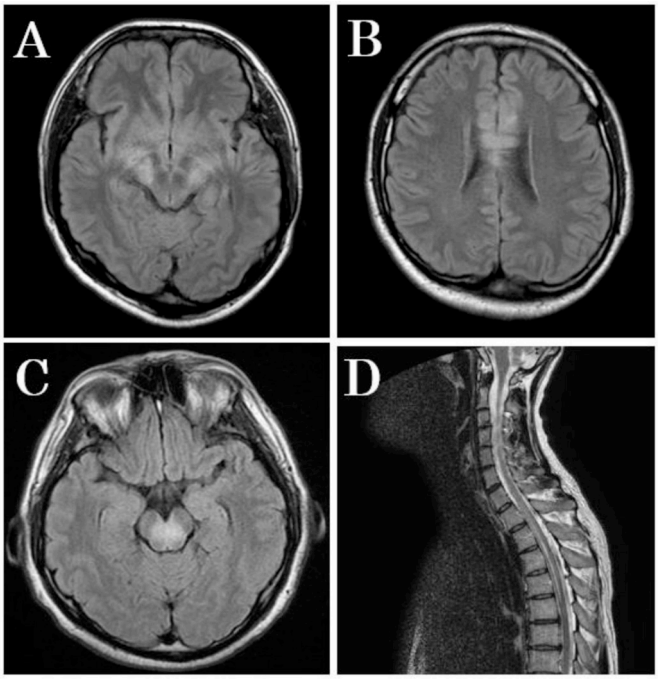

Fig. 5. Representative MRI images of brain, brainstem, and spinal cord lesions in MOG-IgG (+) patients. (A, B) Symmetrical brain lesions are evident in the cerebral peduncles and corpus callosum of a 29-year-old male on fluid-attenuated inversion recovery (FLAIR) imaging. (C) A reversible brainstem lesion is shown in the midbrain of a 32-year-old male by FLAIR imaging; this fully disappeared in a follow-up MRI two weeks later. (D) A longitudinally extensive continuous spinal cord lesion without spinal cord swelling in a 31-year-old male on T2-weighted MRI image.

4. MOG-IgG (+) ON

4.1. MRI characteristics of MOG-IgG (+) ON

As shown in Table 1, the most frequent type of clinical episode in patients with serum MOG-IgG was ON, with the frequency of bilateral ON being much higher than in either the AQP4-IgG (+) or MS groups. Assessment of ON by MRI is usually performed by short-tau inversion recovery, as shown in Fig. 3A. To evaluate whether the ON lesion is in the acute phase and accompanied by inflammation, fat-suppressed contrast-enhanced T1-weighted images are also important (Fig. 3B). It should be noted that MOG-IgG (+) ON can appear as optic perineuritis (Fig. 3C and D) (Akaishi et al., 2016d).

We evaluated the longitudinal length of ON lesions in the acute phase by counting the number of involved optic nerve segments (i.e., anterior orbit, posterior orbit, canalicular, intracranial, chiasmal, and optic tract; Fig. 4A) by MRI (Akaishi et al., 2016c). As shown in Fig. 4B, the ON lesion length in the acute phase of MOG-IgG (+) ON was much longer than that in MS-related ON. These lengths, together with the swollen optic nerves, made the MRI findings in MOG-IgG (+) ON quite prominent; in some cases, the involved optic nerves appeared to be curved in the orbit and constricted in the canalicular segment.

4.2. Comparison of visual prognosis 5 years from the onset of ON

The visual prognoses 5 years after the onset of ON in the three groups are shown in Fig. 4C. The vertical axis shows the corrected visual acuity evaluated by a logMAR scale between 0.0 (best: decimal values $\geq$ 1.0) and 2.0 (worst: decimal values $\leq$0.01). Although the lesion length at the onset of ON is known to affect the eventual visual prognosis in AQP4-Ab (+) ON (Akaishi et al., 2016c), the length in MOG-IgG (+) ON was not significantly correlated with the eventual visual prognosis. Regardless of the length and prominence of acute lesions in MOG-IgG (+) ON, recovery of visual acuity was usually complete if treated with high-dose intravenous steroid pulse therapy. Notably, cases not promptly treated can lose their vision eventually on the affected side, even after a single relapse within years (Akaishi et al., 2016b). In our facility, two patients with MOG-IgG (+) ON were never treated for their ON relapses and lost their vision more than 5 years after their initial attack.

5. MOG-IgG (+) brain and spinal cord lesions

5.1. Brain and brainstem lesions

Although much rarer than isolated ON, brain and brainstem lesions

can present in patients with MOG-IgG (+) disease. Brain lesions in these patients usually do not fulfill the MRI criteria for a diagnosis of MS, and periventricular lesions are quite rare (Polman et al., 2005, Mcdonald et al., 2001). Compared with CNS lesions in MS cases, brain lesions in MOG-IgG (+) cases are paler, fewer, and less prominent; they are sometimes also symmetrical, appearing around the basal ganglia or corpus callosum (Fig. 5A, Fig. 5B) (Akaishi et al., 2016a, 2017).

Brainstem lesions are also seen in MOG-IgG (+) cases, potentially leading to impaired cranial nerve function and severe limb disability if the pyramidal tracts are damaged (Fig. 5C) (Jarius et al., 2016a). When present, medullary lesions may cause intractable hiccups, as can occur in NMOSD, which could persist beyond several days (Akaishi et al., 2016a).

Serum MOG-IgG is sometimes detected in pediatric patients who were previously diagnosed with acute disseminated encephalomyelitis (ADEM) of unknown origin (Kortvelyessy et al., 2017; Reindl and Rostasy, 2015). In our facility, the youngest patient with MOG-IgG (+) disease was aged 2 years old, and he had previously been diagnosed with ADEM. Serum MOG-IgG should be evaluated in all cases of ADEM, irrespective of the age of onset.

Recently, MOG-IgG was reported in some cases of unilateral cerebral cortical encephalitis with epilepsy, all of whom had full recoveries without prolonged epileptic seizures (Ogawa et al., 2017). In these cases, some presentation initially mimicked meningitis, but their CSF and MRI findings were not compatible with either viral or bacterial meningitis. Thus, evaluating serum MOG-IgG levels may also be useful when assessing unilateral encephalo-meningitis of unknown origin.

5.2. Spinal cord lesions

Spinal cord lesions are rarer than either ON or brain lesions, but they are seen in some MOG-IgG (+) cases. Such lesions can be short (≤1 vertebral length) or long (≥3 vertebral lengths). In cases with long spinal cord lesions, such as the case shown in Fig. 5D, the appearance resembles the longitudinally extensive spinal cord lesions of NMO. Lumbosacral spinal cord lesions are also seen in some MOG-IgG (+) cases, but they are very rare in AQP4-IgG (+) cases (Sato et al., 2014).

In on our database, the MSSS after an adequate disease duration in MOG-IgG (+) cases with spinal cord lesions was 0.83 ± 1.71, which was no more severe than observed for other MOG-IgG (+) cases without spinal cord lesions (1.09 ± 1.98; $p \geq 0.10$, Mann–Whitney *U* test). These facts imply that neurological disabilities due to spinal cord lesions in MOG-IgG (+) cases are reversible if treated properly in the acute phase. This differs from the outcomes observed in AQP4-IgG (+) NMOSD cases who usually presents with permanent disability after myelitis.

6. Treatments for MOG-IgG (+) cases

Concerning acute treatment, high-dose intravenous steroid pulse therapy administered in a timely manner undoubtedly improves recovery speed and neurological prognosis in MOG-IgG (+), AQP4-IgG (+), and MS cases (Ontaneda and Rae-Grant, 2009; Kimbrough et al., 2012; Ogawa et al., 2017). This is supported by the fact that some patients MOG-IgG (+) who were not properly treated in the acute phase of ON lose their vision (Akaishi et al., 2016b). Regardless of the much better neurological prognosis in MOG-IgG (+) cases compared with AQP4-IgG (+) NMOSD, such patients should receive timely and appropriate treatment in the acute phase.

In contrast to the clear evidence supporting acute treatment, the benefits of relapse prevention for MOG-IgG (+) cases have yet to be proven. Relapse prevention has been established in MS and NMOSD, however, requiring the long-term use of disease-modifying drugs and immune suppressants (e.g. low-dose oral prednisolone, mycophenolate mofetil), respectively (Jacob et al., 2009). To date, there has been no randomized controlled clinical trial to assess the potential for relapse prevention treatments to help patients with MOG-IgG (+) disease. Although this clearly needs to be addressed, clinical reports and retrospective studies have made some reasonable suggestions, which are worth mentioning (Jarius et al., 2016b).

One common approach to relapse prevention in MOG-IgG (+) cases is the oral administration of low-dose corticosteroids (e.g., prednisolone < 20 mg/day) for several months or years (Pache et al., 2016). In such cases, relatively long-term administration of oral corticosteroids and/or immunesuppressive drugs was shown to be beneficial for reducing the risk of relapses. However, this must be balanced against the fact that some MOG-IgG (+) cases may have a monophasic course becoming seronegative during the following months or years. Therefore, following the serum MOG-IgG titer once every 3 or 6 months to check if they are falling could be used to determine when to stop the relapse prevention treatments. Randomized controlled clinical trials are awaited on the effectiveness of relapse prevention treatments in patients with MOG-IgG (+) disease.

Acknowledgment

This work was supported by JSPS KAKENHI Grant Number JP17K09772

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