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Comparison of myelin oligodendrocyte glycoprotein (MOG)-antibody disease and AQP4-IgG-positive neuromyelitis optica spectrum disorder (NMOSD) when they co-exist with anti-NMDA (N-methyl-D-aspartate) receptor encephalitis

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ABSTRACT

Background: Myelin oligodendrocyte glycoprotein (MOG)-antibody (ab) disease and AQP4-IgG-positive neuromyelitis optica spectrum disorder (NMOSD) can co-exist with anti-NMDA (N-methyl-D-aspartate) receptor encephalitis (NMDARe).

Objectives: To characterize MOG-ab disease and AQP4-IgG-positive NMOSD during NMDARe.

Methods: We analyzed all the patients with overlapping MOG-ab disease and NMDARe (MNOS) and patients with AQP4-IgG-positive NMOSD and NMDARe (ANOS) in our hospital and compared those data with data from systematically review of previously published reports.

Results: In our cohorts, 11.9% patients with MOG-ab disease and 0.6% patients with NMOSD had overlapping NMDARe ($P < 0.01$). After treatment with steroids and/or intravenous immunoglobulin (IVIg), the median modified Rankin Scale (mRS) of the MNOS group decreased significantly during attacks associated with or without NMDARe ($P < 0.01$ for both), while that of the ANOS group did not (attack: $P < 0.05$; attack associated with NMDARe: $P > 0.05$). Analyzed together with previously reported cases, 6% patients with MNOS and 40% patients with ANOS also used rituximab or cyclophosphamide after steroids and/or IVIg ($P < 0.05$) during attacks associated with NMDARe.

Conclusion: Compared with NMOSD, MOG-ab disease may more commonly co-exist with NMDARe. MNOS patients respond better to steroids and IVIg than do ANOS patients during attacks associated with NMDARe.

Introduction

Myelin oligodendrocyte glycoprotein (MOG) is located on the surface of myelin sheaths in the central nervous system (CNS) (Peschl et al., 2017). Extensive research has shown that an autoantibody against MOG (MOG-ab) mediates oligodendrocyte damage and primary demyelination in vitro and in vivo (Dale et al., 2014; Ikeda et al., 2015), suggesting MOG-ab may be a diagnostic biomarker in human demyelinating diseases including multiple sclerosis (MS). However, using traditional methods, such as ELISA and western blot, MOG-ab is

Abbreviations: ab, antibody; ANOS, the overlapping syndrome of AQP4-IgG-positive NMOSD and NMDARe; AQP4, aquaporin-4; CBAs, cell-based assays; CNS, central nervous system; CSF, cerebrospinal fluid; EDSS, Expanded isability Status Scale; IgG, immunoglobulin G; IIFT, immune-fluorescence test; MNOS, the overlapping syndrome of MOG-ab disease and NMDARe; mRS, modified Rankin Scale; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMDA, N-methyl-D-aspartate; NMDARe, NMDA receptor encephalitis; NMOSD, neuromyelitis optica spectrum disorder

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detected in MS, other type of CNS inflammatory diseases, and even in healthy subjects (Ramanathan et al., 2016). More recently, with the development of cell-based assays (CBAs) using the soluble, tetramerized extracellular domain of native MOG as antigen, MOG-ab has regained attention and growing evidence is defining MOG-ab dieses as a new clinical entity (Ramanathan et al., 2016; Sato et al., 2014).

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory autoimmune disease of the CNS with six core clinical characteristics: optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, diencephalic syndrome, and symptomatic cerebral syndrome (Wingerchuk et al., 2015). Aquaporin-4 (AQP4)-immunoglobulin G (IgG) is highly specific for NMOSD diagnosis and has pathogenic potential (Wingerchuk et al., 2015; Lucchinetti et al., 2014). The presence of AQP4-IgG promotes severe immune-mediated astrocyte damage, leading to NMOSD (Lucchinetti et al., 2014).

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis (NMDARe) is an autoimmune encephalitis associated with cerebrospinal fluid (CSF)-IgG against the NR1 subunit of the NMDA receptor. NMDARe often results in a multistage illness that progresses from psychosis, memory deficits, seizures, and language disintegration into a later state of unresponsiveness with catatonic features often associated with abnormal movements and autonomic and breathing instability (Dalmau et al., 2011). Demyelination lesions occasionally occur in NMDARe (Dalmau et al., 2011). MOG-ab disease or AQP4-IgG-seropositive NMOSD can occur simultaneously or sequentially with NMDARe (Titulaer et al., 2014; Kaneko et al., 2014; Hacohen et al., 2014; Zoccarato et al., 2013; Ran et al., 2017; Qin et al., 2017; Luo et al., 2016). However, most of these previous studies were case reports and no study has focused on comparing these two overlapping syndromes with respect to frequency and clinical and paraclinical characteristics.

Herein, we analyzed the frequency, clinical, and laboratory data regarding a clinical series of patients with MOG-ab disease or AQP4-IgG-seropositive NMOSD overlapping with NMDARe. Subsequently, we combined our data with those from previously reported cases.

Materials and methods

Case series study

We conducted a case series study of patients with MOG-ab disease or AQP4-IgG-seropositive NMOSD occurring simultaneously or sequentially with NMDARe. All patient data were obtained from the MSNMOBase, an observational cohort based on prospectively collected data (Xu et al., 2016). The MSNMOBase was developed in the Department of Neurology of Peking Union Medical College Hospital and commenced in 2011. The MOG-ab disease cohort was formed after January 1, 2017 after detection of MOG-ab via CBA became available in our laboratory. At the time of data extraction (September 30, 2017), the MSNMOBase had enrolled 42 patients with MOG-ab disease and 491 patients with NMOSD who met the 2015 NMOSD diagnostic criteria (Wingerchuk et al., 2015). Table 1 summarizes the demographic data. The median onset age of patients with MOG-ab disease were significantly younger than that of patients with NMOSD (12.7 vs. 34.0 years, $P < 0.001$), with a female to male ratio of 24:18 and 445:46, respectively ($P < 0.001$). The median disease duration was 34.8 months (range: 0.8–274.9 months) for patients with MOG-ab disease and 53.1 months (range: 1.0–453.5 months) for NMOSD patients ($P = 0.023$), with a median Expanded Disability Status Scale (EDSS) score of 0 and 2.0 at last follow-up, respectively ($P < 0.001$). All patients with MOG-ab disease were AQP4-IgG seronegative and 435 of 491 (88.6%) patients with NMOSD were AQP4-IgG seropositive. 31 patients with MOG-ab disease and 288 patients with NMOSD had the detection of CSF specific oligoclonal band (SOB), and the positivity of the two groups was 25.8% and 39.6%, respectively ($P = 0.134$).

This study was approved by the ethics committee of Peking Union Medical College Hospital. Patient consent was not required because de-identified data were used in the study.

MOG-ab, AQP-4ab, and anti-NMDAR ab detection

The presence of MOG-IgG, AQP4-IgG, and NMDAR-IgG was evaluated using a fixed cell-based indirect immune-fluorescence test (IIFT) employing Biochips (Euroimmun AG, Lüebeck, Germany). The full-length human MOG and AQP4 isoform M1 and the NR1 subunit of the NMDAR complex were transfected into EU 90 cells and used in the MOG-IgG, AQP4-IgG, and NMDAR-IgG IIFT assays, respectively.

Literature review

We searched PubMed (Medline) through September 30, 2017 for articles published in any language with the search string (“Receptors, N-Methyl-D-Aspartate” [MeSH Terms] OR “N-Methyl-D-Aspartate” OR “NMDA”) AND (“Myelin Oligodendrocyte Glycoprotein” [MeSH Terms] OR “MOG” OR “Neuromyelitis Optica” [MeSH Terms] OR “NMO” OR “Demyelinating Diseases” [MeSH Terms] OR “demyelinating” OR “demyelination”). We also searched the references for related published articles. All obtained articles were reviewed to identify the cases of overlapping MOG-ab disease or AQP4 seropositive NMOSD and NMDARe.

Statistical analysis

Statistical analyses were conducted using the statistical package for the social sciences (SPSS) version 17.0. Data were expressed as medians with ranges or means ± standard deviation (SD) according to the distributions. An analysis of variance (ANOVA), a Student's *t*-test, or a Mann-Whitney test (non-normal distributions) was used for continuous variables. A Pearson $\chi 2$ test or a Fisher's exact test was used for categorical variables. A two-tailed P value < 0.05 was considered statistically significant.

Table 1
Demographic and clinical characteristics of the cohorts of MOG-ab disease and NMOSD.

	MOG ab disease (n = 42)	NMOSD (n = 491)	*P* value
Inclusion age, median (range), years	17.8 (3.7–56.1)	42.0 (5.8–85.1)	< **0.001**
Age at onset, median (range), years	12.7 (2.5–55.8)	34.0 (0.8–76.6)	< **0.001**
Female, % (n/total)	57.1 (24/42)	90.6 (445/491)	< **0.001**
Disease duration, median (range), mo.	34.8 (0.8–274.9)	53.1 (1.0–453.5)	**0.023**
EDSS at last follow-up, median (range)	0.0 (0.0–3.0)	2.0 (0.0–9.5)	< **0.001**
AQP4-IgG positive, % (n/total)	0 (0/42)	88.6 (435/491)	< **0.001**
CSF SOB positive, % (n/total)	25.8 (8/31)	39.6 (114/288)	0.134
NMDARe, % (n/total)	11.9 (5/42)	0.6 (3/491)	< **0.001**

ab = antibody; AQP4 = aquaporin 4; CSF = cerebrospinal fluid; EDSS = expanded disability status scale; IgG = immunoglobulin G; mo. = month; NMDARe = anti-N-methyl-D-aspartate receptor encephalitis; NMOSD = neuromyelitis optica spectrum disorders; n = number; SOB = specific oligoclonal band.

Table 2
Demographic, clinical and neuroimaging findings in 8 patients with overlapping MOG-ab disease or NMOSD and NMDARe.

Case No.	Sex/Age at Onset, y	Ep. No.	Clinical Syndrome	Interval mo.	Presenting Manifestations	MRI Findings (Brain / Spine)	Immunotherapy	mRS max	mRS after Ep.
Patients with overlapping MOG-ab disease and NMDARe									
1	F/3	1	DSE	–	BON	n.a.	Short-term DEXA	2	0
		2	NMDARe & DSE	240	Headache, short-term memory loss, depressed mood, verbal reduction and lethargy	T2 hyperintensity with partial enhancement in left basal ganglion, hypothalamus, and bilateral thalami	High dose IV MP, oral st taper	2	1
		3	NMDARe & DSE	12	Verbal reduction, social withdrawal, fear, persecutory delusion, and irritability	New T2 hyperintensity lesion in left pontis / normal	IVIg, oral st taper, MMF	3	1
2	M/23	1	DSE	–	Dizziness, headache, severe insomnia, and seizure	T2 hyperintensity in right cerebral peduncle	High dose IV MP, oral st taper	2	1
		2	DSE	24	Vertigo, diplopia, unsteady walk, and seizure	New T2 hyperintensity lesions with partial enhancement in left pontis, thalamus and parietal lobe	High dose IV MP, oral st taper	2	1
		3	NMDARe & DSE	20	Dizziness, severe insomnia, temper tantrums, memory loss, and self-degradation	New T2 hyperintensity lesions with partial enhancement in left cerebellar, bilateral frontal lobes, right parietal lobe, and corpus callosum / normal	IVIg, oral st taper, MMF	3	1
3	M/6	1	NMDARe & DSE	–	Verbal reduction, irritability, stereotyped actions, memory loss; later: recurrent seizures, coma, and hypoventilation	T2 hyperintensity in bilateral temporal and parietal lobes, and bilateral basal ganglia	IVIg, high dose IV MP, oral st taper	5	0
		2	NMDARe & DSE	12	Similar to the first Ep.	New T2 hyperintensity lesion in bilateral frontal lobes / Intramedullary T2 hyperintensity lesion	IVIg, high dose IV MP, oral st taper	5	0
		3	NMDARe & DSE	6	Similar to the first Ep.	NewT2 hyperintensity lesions in right cerebral peduncle, left basal ganglion, and bilateral frontal lobes	High dose IV MP, oral st taper, IVIg once per mo. for 6 months	5	0
		4	NMDARe & DSE	18	Similar to the first Ep.	New T2 hyperintensity lesions in bilateral temporal, frontal and insular lobes, bilateral thalami, right optic tract, left cerebral peduncle and pontis.	High dose IV MP, IVIg, RTX, oral st taper	5	0
		5	NMDARe & DSE	18	Similar to the first Ep.	New T2 hyperintensity lesions in right frontal and parietal lobes.	High dose IV MP, IVIg, oral st taper, MMF	5	0
4	M/25	1	NMDARe & DSE	–	Headache, seizures, visual hallucination	T2 hyperintensity along the cortex of right hemisphere.	High dose IV MP, oral st taper	2	0
5	M/9	1	NMDARe	–	Abnormal behavior, irritability, memory loss; later: recurrent seizures, stupor, coma, and hypoventilation	T2 hyperintensity along the cortex of left temporal lobe.	High dose IV MP, IVIg, oral st taper, MMF	5	0
		2	NMDARe & DSE	18	Aphasia, ON	Normal.	IVIg, oral st taper	2	0
Patients with overlapping NMOSD and NMDARe									
6	F/62	1	NMDARe & NMOSD	–	Lethargy, verbal reduction, abnormal behavior, central hypoventilation, AM; later: mutism	T2 hyperintensity lesions in left periventricular white matter, bilateral frontal lobes, hypothalamus, and left thalamus, with partial enhancement / normal	High dose IV MP, IVIg, oral st taper, MMF	5	4
7	F/16	1	NMDARe	–	Fever, headache, dysphasia, psychosis, memory loss, cognitive decline	T2 hyperintensity lesions in bilateral basal ganglia and bilateral thalamus; with T2 hypointensity and partially enhanced lesion in the left basal ganglion / normal	High dose IV MP, oral st taper	4	1
		2	NMOSD	20	AM	T2 hyperintensity lesions in left basal ganglion, thalamus, hippocampus, and cerebral peduncle	High dose IV MP, oral st taper	2	1
		3	NMOSD	12	ABS	New onset T2 hyperintensity lesions in left thalamus, and cerebral peduncle	High dose IV MP, oral st taper	2	1
		4	NMOSD	5	ABS	New T2 hyperintensity lesions around cerebral aqueduct	IVIg, high dose IV MP, oral st taper, MMF	3	1
8	F/25	1	NMDARe	–	Verbal reduction, irritability, abnormal behavior, psychosis, seizure	T2 hyperintensity lesions in pons, right temporal lobe, hippocampus, periventricular white matter	High dose IV st, oral st taper	4	1
		2	NMDARe & NMOSD	6	Irritability, ABS	New T2 hyperintensity lesions in brainstem, left hippocampus	High dose IV st, oral st taper	3	2
		3	NMDARe & NMOSD	5	Short-term memory loss, psychosis, ABS	New T2 hyperintensity lesions in left basal ganglion, hippocampus and medial temporal lobe, and right thalamus	IVIg, high dose IV MP, oral st taper, CTX	3	3
		4	NMDARe	18	Lethargy, memory loss, personality change	New T2 hyperintensity lesions in brainstem	IVIg, oral st taper, MMF (0.5 g bid)	3	3

(*continued on next page*)

Table 2 (*continued*)

Case No.	Sex/Age at Onset, y	Ep. No.	Clinical Syndrome	Interval mo.	Presenting Manifestations	MRI Findings (Brain / Spine)	Immunotherapy	mRS max	mRS after Ep.
		5	NMOSD	20	ON, ABS	T2 hyperintensity lesions in right cerebellum / normal	IVIg, oral st taper, MMF (0.75 g bid)	4	4

Tumor was not detected in these 8 patients after thorough screening.

ABS = acute brainstem syndrome; AES = acute diencephalic syndrome; AM = acute myelitis; BON = bilateral optic neuritis; DEXA = dexamethasone; DSE = demyelination syndrome episode; Ep. = episode; F = female; IV = intravenous; IVIg = intravenous immunoglobulin; M = male; MMF = mycophenolate mofetil; mo. = month; MOG = myelin oligodendrocyte glycoprotein; MP = methylprednisolone; MRI = magnetic resonance imaging; mRS = modified Rankin scale; n.a. = not applicable; NMDARe = anti-N-methyl-D-aspartate receptor encephalitis; NMOSD = neuromyelitis optica spectrum disorders; No. = number; RTX = rituximab; ON = optic neuritis; st = steroids; y. = year.

Results

Results from case series study

Five of forty-two (11.9%) patients with MOG-ab disease (cases 1–5; four males, one female) and 3 of 491 (0.6%) patients with NMOSD (cases 6–8, three females) also had NMDARe (Table 1, $P < 0.001$). All eight patients fulfilled the diagnostic criteria for definite NMDARe (Graus et al., 2016) and we diagnosed the NMDARe mainly depending on the CSF NMDAR-IgG. Patients with overlapping NMOSD and NMDARe were AQP4-IgG seropositive and MOG-ab seronegative. The overlapping syndrome of MOG-ab disease and NMDARe was abbreviated as MNOS; the overlapping syndrome of AQP4-IgG-positive NMOSD and NMDARe was abbreviated as ANOS.

The onset age ranged from 3 to 25 years for patients with MNOS, and 16–62 years for patients with ANOS. Three of five patients with MNOS and no patients with ANOS started the disease as children (< 14 years). All eight patients were previously healthy and none had tumors. In patients with MNOS, NMDARe occurred prior to the episode of MOG-ab disease in one patient (case 5, 18 months), simultaneously in two patients (cases 3 and 4), and after the episode of MOG-ab disease in two patients (cases 1 and 2, 44–240 months). In patients with ANOS, NMDARe occurred before the episode of NMOSD in two patients (cases 7 and 8, 6–20 month) and simultaneously in one patient (case 6) (Table 2).

Brain magnetic resonance imaging (MRI) was performed in all eight patients (Figs. 1 and 2, Table 2). Spinal cord MRI was performed in all eight patients except for cases 4 and 5, who had no sign of spinal cord impairments (Table 2). All eight patients had supratentorial lesions; three of five patients with MNOS (cases 1–3) and two of three patients with ANOS (cases 7 and 8) had infratentorial lesions. However, only one patient with MNOS (case 3) and no patients with ANOS had spinal cord lesions. Table 3 summarizes the laboratory findings of the patients. No differences in CSF or serum results were found between the two groups.

High doses of steroids and intravenous immunoglobulin (IVIg) were the main treatment for attacks in both groups. In patients with MNOS, we recorded 14 attacks of which 10 were related to NMDARe. In patients with ANOS, we recorded 10 attacks of which 6 attacks were related to NMDARe. For total attacks, the median (range) modified Rankin Scale (mRS) of both groups was 3 (2 − 5) before treatment. After treatment, the median (range) mRS significantly decreased to 0 (0 − 1) in the MNOS group ($P = 0.001$) and 2 (1 − 4) in the ANOS group ($P = 0.016$). The median mRS in the MNOS group was significantly lower than that in the ANOS group ($P < 0.001$) (Fig. 3A). For attacks related to NMDARe, no differences in median (range) mRS were found between the two groups before treatment [MNOS: 5 (2 − 5); ANOS: 4 (3 − 5); $P = 0.808$]. After treatment, the median (range) mRS significantly decreased to 0 (0 − 1) in the MNOS group ($P = 0.003$), but that of the ANOS group (3; 1–4) did not decrease significantly ($P = 0.063$) (Fig. 3B).

Results from a systematic review of the literature

The initial literature search yielded 198 published reports. We reviewed the reports and their references for related published reports and identified another 11 patients with MNOS (Titulaer et al., 2014; Kaneko et al., 2014; Yokoyama et al., 2016) and 14 patients with ANOS (Titulaer et al., 2014; Zoccarato et al., 2013; Ran et al., 2017; Qin et al., 2017; Luo et al., 2016; Honda and Yuasa, 2008; Watanabe et al., 2014) after exclusion criteria were applied. Cases with negative MOG-ab and AQP4-ab tests or unreported results were excluded. Two cases were excluded because the symptoms of NMDARe were absent, although anti-NMDAR ab was positive. The characteristics of these previously reported patients, along with our eight patients are summarized in Table 4.

Compared with the patients with ANOS, the patients with MNOS

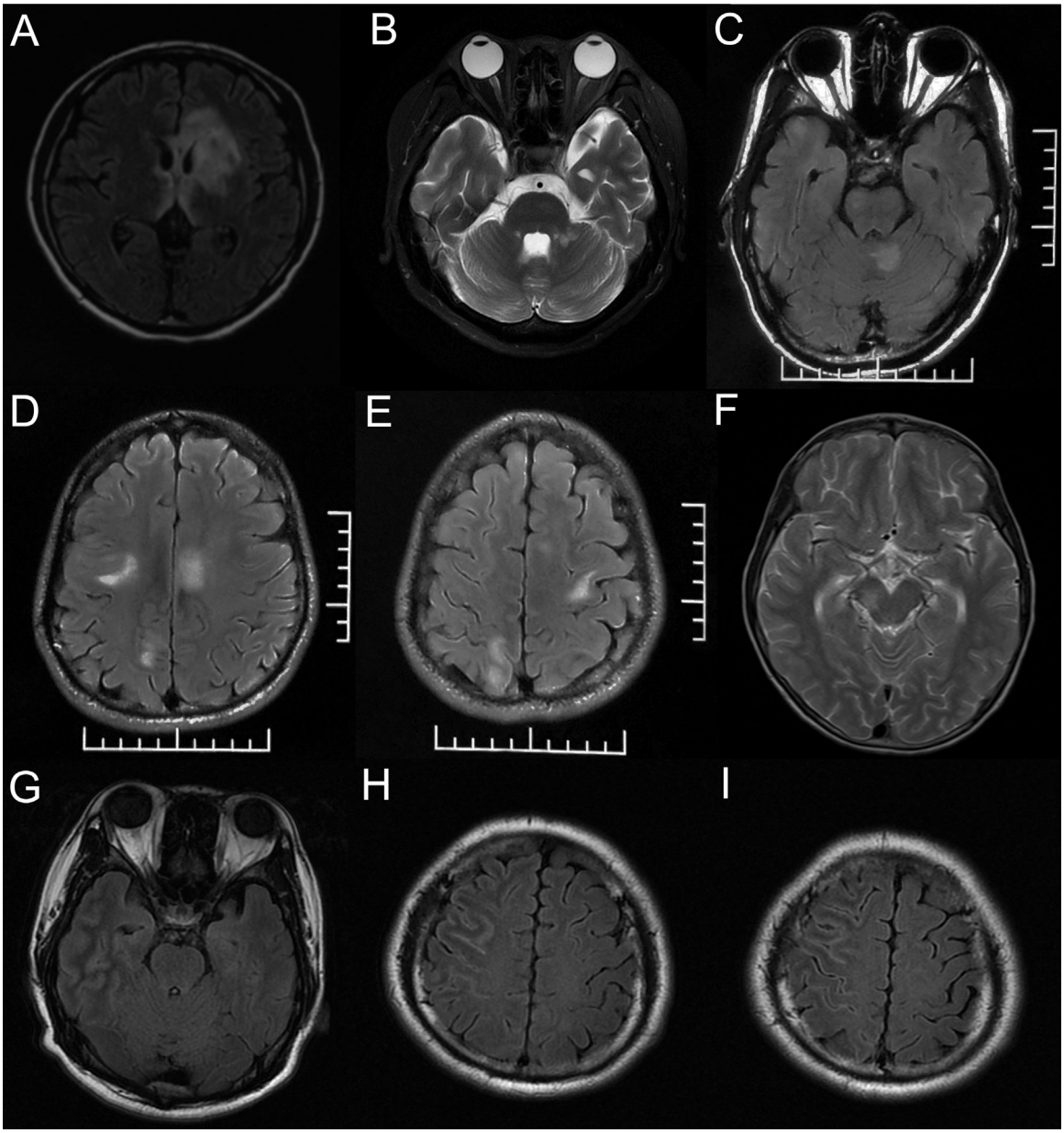

Fig. 1. Brain MRI of the patients with overlapping myelin oligodendrocyte glycoprotein-antibody disease and anti-N-methyl-D-aspartate receptor encephalitis. Brain MRI for the 2nd episode of case 1 showed fluid attenuated inversion recovery (FLAIR) hyperintensity in left basal ganglion, bilateral thalami, corpus collosum, and periventricular white matters (A). Brain MRI for the 3rd episode of case 1 revealed T2 hyperintensity in left pontis (B). Brian MRI for the 3rd episode of case 2 showed FLAIR hyperintensity in left cerebellum (C), and bilateral frontal lobes, parietal lobe and corpus callosum (D, E). Brain MRI for the 3rd episode of case 3 showed T2 hyperintensity lesions in right cerebral peduncle (F). Brain MRI for case 4 showed FLAIR hyperintensity along the cortex of right hemisphere (G, H, I).

were significantly younger at onset (20 years vs. 32 years, $P = 0.029$). A significantly higher percentage of MNOS patients started disease in children ($\leq$ 14 years) (44% vs. 6%, $P = 0.017$). A significantly lower percentage of MNOS patients were female (38% vs. 94%, $P < 0.001$). Similar percentages of MNOS and ANOS patients were of East Asian descent (69% vs. 59%, $P = 0.721$) and had a tumor(s) (0 vs. 6%, $P = 1.000$).

No significant differences in features of episodes or symptoms were found between the patients with MNOS and ANOS. Psychiatric behavior or cognitive dysfunction was the most common symptoms of NMDARe in both overlapping syndromes (75% vs. 88%, $P = 0.398$).

In MRI findings, 100% of MNOS patients and 94% of ANOS patients had supratentorial lesions ($P = 0.157$). Further, 35% of ANOS patients had medial temporal lobe or hippocampus lesions, which was significantly higher than for the patients with MNOS (6%, $P = 0.041$). No differences in infratentorial or spinal cord lesions were found between the two overlapping syndromes. In CSF findings, no differences in percentage of SOB positivity was found between the two overlapping syndromes (56% vs. 69%, $P = 0.474$).

In terms of treatments for attacks, steroids and IVIg were the most common fist-line therapies in both overlapping syndromes regardless of whether the episodes were related to NMDARe. Compared with patients with MNOS, patients with ANOS were more likely to be treated with second-line therapy (including rituximab or cyclophosphamide) in an episode of NMDARe (40% vs. 6%, $P = 0.025$). As for prognosis, more patients with MNOS had good outcomes (last mRS ≤ 2) compared with patients with ANOS (94% vs. 50%, $P = 0.006$).

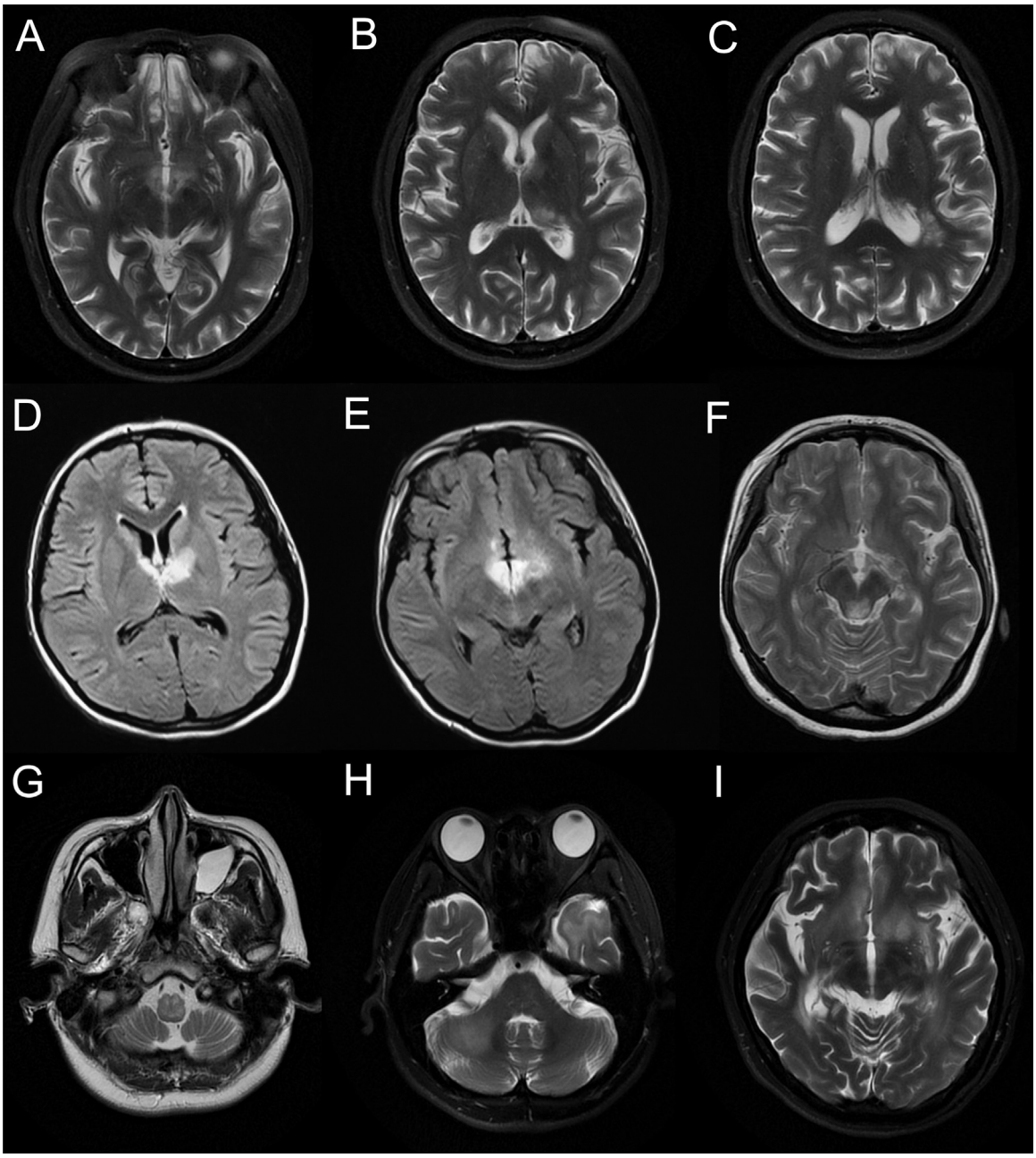

Fig. 2. Brain MRI of the patients with overlapping aquaporin-4 antibody seropositive neuromyelitis optica spectrum disorder and anti-N-methyl-D-aspartate receptor encephalitis. Brain MRI for case 6 showed T2 hyperintensity lesions in bilateral frontal lobes, hypothalamus (A), left thalamus (B), and left periventricular white matter (C). Brain MRI for the 1st episode of case 7 showed fluid attenuated inversion recovery (FLAIR) hyperintensity lesions in bilateral basal ganglia (D), thalamus and hypothalamus (E). Brain MRI for the 4th episode of case 7 showed T2 hyperintensity lesions around cerebral aqueduct (F). Brain MRI for case 8 showed hyperintensity lesions in medulla (G), right cerebellum (H), bilateral frontal lobes, left insula and periventricular white matter (I).

Discussion

This study provides new evidence indicating that MOG-ab disease may be an independent clinical entity. In observed patients, MOG-ab disease more commonly co-exists with NMDARe, responds better to steroids and IVIg during the acute phase of episodes when associated with NMDARe, and has a better prognosis than AQP4-IgG-positive NMOSD. In addition, MOG-ab disease may also be prevalent in populations of Eastern Asian descent.

In our cohorts, 11.9% of patients with MOG-ab disease also had NMDARe, which was significantly higher than in patients with NMOSD (0.6%, $P < 0.001$). Thus, MOG-ab disease may be distinct from AQP4-IgG-positive NMOSD and may have different pathogenesis for co-existing with NMDARe. The idea that MOG-ab disease and AQP4-IgG-positive NMOSD are different clinical entities was suggested by recent evidence, including clinical and radiological features (Sato et al., 2014; Siritho et al., 2016; Jarius et al., 2016a, 2016b; Kitley et al., 2014; Jurynczyk et al., 2017) and attacking targets. The MOG-ab causes oligodendrocyte damage and primary demyelination without astrocyte loss, leading to oligodendrocytopathy (Ikeda et al., 2015; Dale et al., 2014; Wang et al., 2016), while AQP4-ab promotes immune-mediated astrocyte damage and leads to astrocytopathy (Lucchinetti et al., 2014; Wang et al., 2016). It is unknown why MOG-ab disease is relatively frequently associated with NMDARe, but it should be noted that oligodendrocytes contain NMDAR (Lipton, 2006). Future studies will determine how the interaction of these two abs (MOG-IgG and NMDAR-

Table 3
Laboratory findings in 8 patients with overlapping MOG-ab disease or NMOSD and NMDARe during representative attacks.

Case No.	Ep. No.	CSF WBC (μL)	CSF Pro (g/L)	CSF SOB	NMDAR-ab (dilution), CSF/Serum	MOG-ab (dilution), CSF/Serum	AQP4-ab (dilution), CSF/Serum
Patients with overlapping MOG-ab disease and NMDARe							
1	3	0	0.26	Negative	Positive (1:32) / negative	Positive (1:32) / positive (1:100)	Negative / negative
2	3	0	0.36	Positive	Positive (1:100) / negative	Negative / positive (1:100)	Negative / negative
3	5	8	0.28	Positive	Positive (1:100) / positive (1:32)	Negative / positive (1:100)	Negative / negative
4	1	96	0.49	Positive	Positive (1:10) / negative	Positive (1:100) / positive (1:320)	Negative / negative
5	2	2	0.29	Positive	Positive (1:100) / negative	Negative / positive (1:100)	Negative / negative
Patients with overlapping NMOSD and NMDARe							
6	1	7	0.69	Positive	Positive (1:100) / negative	Negative /negative	Positive (1:1) / positive (1:32)
7	2	5	0.45	Positive	Positive (1:32) / negative	n.a. / n.a.	Positive (n.k.) / positive (n.k.)
	4	3	0.39	Positive	Positive (1:1) / negative	n.a. / n.a.	Positive (1:1) / positive (1:32)
8	4	0	0.27	Positive	Positive (1:10) / negative	n.a. / n.a.	n.a. / negative
	5	2	0.37	Positive	Positive (1:1) / negative	Negative /negative	Negative /positive (1:10)

The antibodies results represent the first available result of each episode.
ab = antibody; CSF = cerebrospinal fluid; Ep. = episode; MOG = myelin oligodendrocyte glycoprotein; n.a. = not applicable; n.k. = not known; NMDAR = anti–N-methyl-D-aspartate receptor; No. = number; Pro = protein; SOB = specific oligoclonal band; WBC = white blood cell.

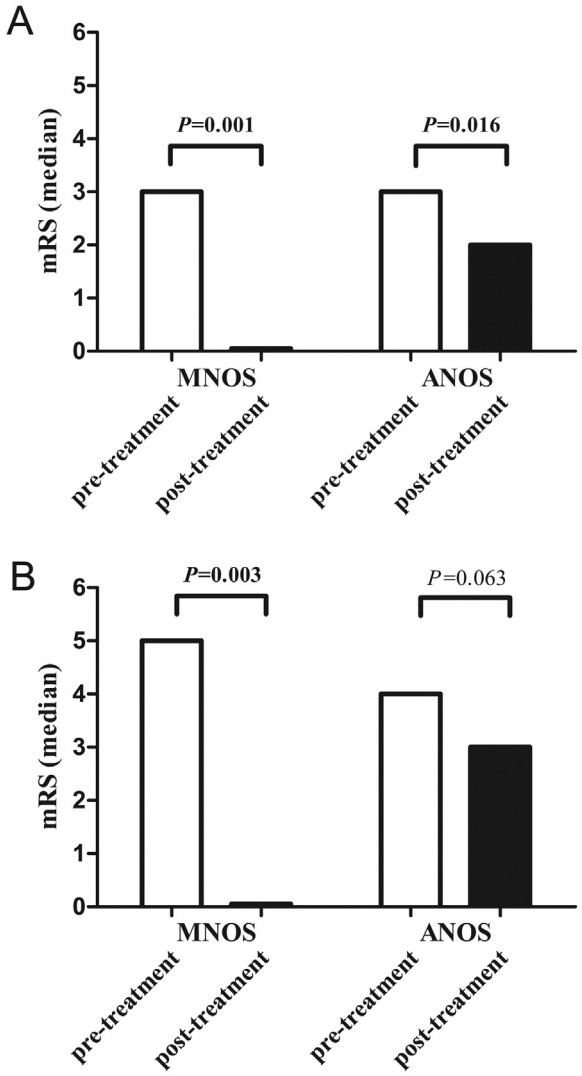

Fig. 3. The comparison of the median modified Rankin scale (mRS) scores in patients with overlapping syndrome of myelin oligodendrocyte glycoprotein-antibody disease and anti-NMDA receptor encephalitis (MNOS) and patients with AQP4-IgG positive neuromyelitis optica spectrum disorder and anti-NMDA receptor encephalitis (ANOS) between pre-treatment and post-treatment. When all episodes were analyzed together, mRS decreased significantly in both groups (MNOS and ANOS) (A). When episodes with anti-NMDA receptor encephalitis were analyzed, mRS decreased significantly in patients with MNOS, while there was no significant change in mRS of patients with ANOS (B).

IgG) function in the pathogenesis. All three patients with ANOS were AQP4-IgG seropositive. This result corroborates findings from previous studies that AQP4-IgG-positive NMOSD was associated with other organ-specific or systemic autoimmune diseases, such as anti-acetylcholine receptor-positive myasthenia gravis (Leite et al., 2012), autoimmune thyroid disease (Pittock et al., 2008), primary Sjogren's syndrome, and systemic lupus erythematosus (Asgari et al., 2017), further indicating a general susceptibility to antibody-mediated autoimmune disease (Pittock et al., 2008).

Analysis of previously reported cases together indicated that most patients with MNOS (69%) were of East Asian descent, which was similar to the patients with ANOS (59%). Thus, ethnic differences may exist in the incidence of MOG-ab diseases, like in NMOSD which occur more often in populations of African, East Asian, and Latin American descent than in other groups (Asgari et al., 2011). However, there are no data regarding the prevalence of MOG-ab disease currently. Further epidemiological and genetic study of MOG-ab disease based on the standard detection method (CBA) is needed for a comprehensive understanding of the disease.

Different from pure MOG-ab disease or NMOSD, patients with MNOS or ANOS had symptoms related to encephalitis. Among these symptoms, psychiatric behaviors or cognitive dysfunction were the most common (Table 4). Moreover, these symptoms were frequently milder than in typical NMDARe. Most patients with MNOS or ANOS did not progress to a final state of unresponsiveness, and the frequency of unconsciousness was low (Table 4, 25% and 35%, respectively) compared to typical NMDARe with approximately 60% of patients progressing to unconsciousness (Titulaer et al., 2013).

Two-thirds of patients with MOG-ab disease (Jarius et al., 2016b; Zhou et al., 2017; Kim et al., 2015) or NMOSD (Wingerchuk et al., 2015; Kim et al., 2010) have brain lesions, and most of these lesions are infratentorial. However, in combining our data with previously reported cases, 100% of patients with MNOS and 94% of patients with ANOS had supratentorial lesions. Therefore, in patients with MOG-ab disease or NMOSD that exhibit psychiatric behaviors or cognitive dysfunction and supratentorial lesions, the co-existence of NMDARe should be considered and anti-NMDA receptor ab expression should be evaluated.

Tumors (usually ovarian teratoma) are one of the most common known immunologic triggers of NMDARe (Titulaer et al., 2013). Approximately 50% of young women with NMDARe have ovarian teratoma (Titulaer et al., 2013). However, none of our patients with MNOS or ANOS were diagnosed with tumors after thorough tumor screening. Together with previously reported cases, there were 13 young women (13–45 years) evaluated and only one case with ANOS had an ovarian teratoma (Table 4); this ratio was much lower than that of typical NMDARe (50%) (Titulaer et al., 2013). Therefore, tumors are not likely

Table 4
Comparison of clinical and paraclinical data between patients with two overlapping syndromes.

Characteristics	MNOS (n = 16)	ANOS (n = 17)	*P* value
Age at onset, median (range), y	20 (3–48)	32 (8–62)	**0.029**[f]
≤ 14 (pediatric patients), n (%)	7 (44%)	1 (6%)	**0.017**[e]
Sex (Female), n (%)	6 (38%)	16 (94%)	**< 0.001**[e]
Ethnicity (East Asian), n (%)	11 (69%)	10 (59%)	0.721
First episode			
MOG-ab disease / NMOSD, n (%)	5 (31%)	6 (35%)	0.428
NMDARe, n (%)	7 (44%)	4 (24%)	
MOG-ab disease / NMOSD and NMDARe, n (%)	4 (25%)	7 (41%)	
Time interval[g]			
First episode: MOG-ab disease / NMOSD (mean ± SD, mo.)	90.0 ± 88.1	35.8 ± 33.1	0.286
First episode: NMDARe (mean ± SD, mo.)	8.3 ± 7.5	44.0 ± 84.5	0.327
Episode times, median (range)	3 (1–6)	2 (1–5)	0.309
Symptoms of NMDARe			
Abnormal behavior or cognitive dysfunction, n (%)	12 (75%)	15 (88%)	0.398
Speech dysfunction	4 (25%)	6 (35%)	0.708
Seizure	8 (50%)	5 (29%)	0.296
Movement disorder, dyskinesia or rigidity posture	6 (38%)	5 (29%)	0.721
Decreased level of consciousness	4 (25%)	6 (35%)	0.708
Autonomic dysfunction or central hypoventilation	5 (31%)	5 (29%)	1.000
Supratentorial lesion	16 (100%)	15 (94%)	0.157
Medial temporal lobe or hippocampus	1 (6%)	6 (35%)	**0.041**[e]
Corpus collosum	2 (13%)	0	0.107
Basal ganglia	5 (31%)	9 (53%)	0.208
Thalamus	5 (31%)	5 (29%)	0.909
Hypothalamus	3 (19%)	4 (24%)	0.737
Infratentorial lesion or spinal cord lesion, n (%)[h]	9[a] (56%)	11[a] (65%)	0.548
Infratentorial lesion	9 (56%)	8 (47%)	0.598
Spinal cord lesion	5 (31%)	7 (41%)	0.899
SOB positive	9 (56%)	9[a] (69%)	0.474
Tumor	0	1[b] (6%)	1.000
Treatment (DSE/NMOSD w or w/o NMDARe), n (%)			
Steroids	14 (88%)	14[c] (93%)	0.583
IVIg	8 (50%)	9[c] (60%)	0.576
PE	1 (6%)	5[c] (33%)	0.056
RTX or CTX	3 (19%)	4[c] (27%)	0.598
Treatment (NMDARe w or w/o DSE/NMOSD), n (%)			
Steroids	15 (94%)	13[c] (87%)	0.505
IVIg	7 (44%)	11[c] (73%)	0.095
PE	1 (6%)	4[c] (27%)	0.122
RTX or CTX	1 (6%)	6[c] (40%)	**0.025**[e]
Good outcome (last mRS ≤ 2), n (%)	15 (94%)	8[d] (50%)	**0.006**[e]

ab = antibody; ADEM = acute disseminated encephalomyelitis; CSF = cerebrospinal fluid; CTX = cyclophosphamide; DSE = demyelination syndrome episode; F = female; M = male; MOG = myelin oligodendrocyte glycoprotein; MRI = magnetic resonance imaging; mRS = modified Rankin Scale; n = number; NMDARe = anti–N-Methyl-D-Aspartate receptor encephalitis; NMOSD = neuromyelitis optica spectrum disorders; PE = plasma exchange; RTX = rituximab; SD = standard deviation; SOB = specific oligoclonal band; w or w/o = with or without; y. = year.

[a] 4 Patients unknown.

[b] Ovarian teratoma.

[c] 2 Patients unknown.

[d] 2 Patients unknown, 1 patient died.

[e] *P* value (Pearson χ^2 test) < 0.05.

[f] *P* value (Mann-Whitney test) < 0.05.

[g] Time interval refers to the time interval between the first episode of DSE/NMOSD and the first episode of NMDARE or vice versa.

[h] When the frequency of the presence of spinal cord lesions was calculated, the denominators were assumed to be 16 for patients with overlapping MOG ab disease and NMDARe, and 17 for patients with overlapping NMOSD and NMDARe.

the main trigger of NMDARe in MNOS and ANOS patients. Titulaer et al. suggested that autoimmunity, and not tumors, trigger the disorders that overlap demyelinating syndromes with NMDARe (Titulaer et al., 2014).

High-dose steroids and IVIg were the main treatments utilized during attacks in our eight patients. The median mRS in both groups following treatment of attacks decreased significantly (Fig. 3), but the degree of decrease in the MNOS group was larger than that in the ANOS group. For attacks associated with NMDARe, the median mRS following treatment in the MNOS group also decreased significantly, while the median mRS in the ANOS group did not decrease. Thus, patients with MNOS responded better to steroids and/or IVIg than did the patients with ANOS during the acute phase of episodes. Combining our data with previously reported cases indicated that more patients with ANOS than with MNOS also used the second-line treatment (rituximab and cyclophosphamide) after the first-line treatment (high-dose steroids and IVIg) during attacks related to NMDARe (Table 4, 40% vs. 6%, $P = 0.025$). This further suggests that the MNOS group responded better to first-line treatments, especially when attacks were related to NMDARe, compared to the ANOS group.

A limitation of this study was the small number of cases available for evaluation due to the rarity of this group of patients; additionally, many of the previously reported cases were from a single study (Titulaer et al., 2014). Retrospective design is another limitation, as it entails some methodological limitations such as inconsistent and incomplete sampling (e.g. CSF examination). Furthermore, the time of follow-up was short because detection of MOG-ab via CBA became available in our laboratory only recently. Therefore, we may have missed some differences between these two overlapping syndromes, such as the CSF characteristics and the effect of long-term treatment

with immunosuppressants. Future prospective, multicenter studies that include CSF examination during every attack and regular assessment of mRS with longer follow-ups are warranted.

Conclusions

MOG-ab disease and NMOSD can co-exist with NMDARe. The co-existence of NMDARe should be considered when patients with MOG-ab disease or NMOSD have unusual symptoms (especially psychiatric behaviors or cognitive dysfunction) and supratentorial lesions. Compared with NMOSD, MOG-ab disease may more commonly co-exist with NMDARe and may result from different immune mechanisms. With co-existing NMDARe, patients with MOG-ab disease responded well to high-dose steroids and IVIg during attacks associated with NMDARe, while patients with NMOSD more often needed the second-line treatment, such as rituximab or cyclophosphamide.

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Conflicts of interest statement

All authors declared that they have no conflicts of interest.

References

Asgari, N., Jarius, S., Laustrup, H., et al., 2017. Aquaporin-4-autoimmunity in patients with systemic lupus erythematosus: a predominantly population-abased study. Mult. Scler. http://dx.doi.org/10.1177/1352458517699791.

Asgari, N., Owens, T., Frøkiær, J., Stenager, E., Lillevang, S.T., Kyvik, K.O., 2011. Neuromyelitis optica (NMO) - an autoimmune disease of the central nervous system (CNS). Acta Neurol. Scand. 123, 369–384.

Dale, R.C., Tantsis, E.M., Merheb, V., et al., 2014. Antibodies to MOG have a demyelination phenotype and affect oligodendrocyte cytoskeleton. Neurol. Neuroimmunol. Neuroinflamm. 1, e12.

Dalmau, J., Lancaster, E., Martinez-Hernandez, E., Rosenfeld, M.R., Balice-Gordon, R., 2011. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 10, 63–74.

Graus, F., Titulaer, M.J., Balu, R., et al., 2016. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 15, 391–404.

Hacohen, Y., Absoud, M., Hemingway, C., et al., 2014. NMDA receptor antibodies associated with distinct white matter syndromes. Neurol. Neuroimmunol. Neuroinflamm. 1, e2.

Honda, K., Yuasa, T., 2008. A case of anti-aquaporin-4 and anti-glutamate receptor antibodies positive myelitis presented with modest clinical signs. Magn. Reson. Med. Sci. 7, 55–58.

Ikeda, K., Kiyota, N., Kuroda, H., et al., 2015. Severe demyelination but no astrocytopathy in clinically definite neuromyelitis optica with anti-myelin-oligodendrocyte glycoprotein antibody. Mult. Scler. 21, 656–659.

Jarius, S., Ruprecht, K., Kleiter, I., et al., 2016a. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. J. Neuroinflamm. 13, 279.

Jarius, S., Ruprecht, K., Kleiter, I., et al., 2016b. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. J. Neuroinflamm. 13, 280.

Jurynczyk, M., Geraldes, R., Probert, F., et al., 2017. Distinct brain imaging characteristics of autoantibody-mediated CNS conditions and multiple sclerosis. Brain 140, 617–627.

Kaneko, K., Sato, D.K., Misu, T., et al., 2014. Anti-N-methyl-D-aspartate receptor encephalitis with multiphasic demyelination. Ann. Neurol. 76, 462–464.

Kim, S.M., Woodhall, M.R., Kim, J.S., et al., 2015. Antibodies to MOG in adults with inflammatory demyeliating disease of the CNS. Neurol. Neuroimmunol. Neuroinflamm. 2, e163.

Kim, W., Park, M.S., Lee, S.H., et al., 2010. Characteristic brain magnetic resonance imaging abnormalities in central nervous system aquaporin-4 autoimmunity. Mult. Scler. 16, 1229–1236.

Kitley, J., Waters, P., Woodhall, M., et al., 2014. Neuromyelitis optica spectrum disorders with aquaporin-4 and myelin-oligodendrocyte glycoprotein antibodies: a comparative study. JAMA Neurol. 71, 276–283.

Leite, M.I., Coutinho, E., Lana-Peixoto, M., et al., 2012. Myasthenia gravis and neuromyelitis optica spectrum disorder: a multicenter study of 16 patients. Neurology 78, 1601–1607.

Lipton, S.A., 2006. NMDA receptors, glial cells, and clinical medicine. Neuron 50, 9–11.

Lucchinetti, C.F., Guo, Y., Popescu, B.F., Fujihara, K., Itoyama, Y., Misu, T., 2014. The pathology of an autoimmune astrocytopathy: lessons learned from neuromyelitis optica. Brain Pathol. 24, 83–97.

Luo, J.J., Lv, H., Sun, W., et al., 2016. Anti-N-methyl-d-aspartate receptor encephalitis in a patient with neuromyelitis optica spectrum disorders. Mult. Scler. Relat. Disord. 8, 74–77.

Peschl, P., Bradl, M., Hoftberger, R., Berger, T., Reindl, M., 2017. Myelin oligodendrocyte glycoprotein: deciphering a target in inflammatory demyelinating diseases. Front Immunol. 8, 529.

Pittock, S.J., Lennon, V.A., de Seze, J., et al., 2008. Neuromyelitis optica and non organ-specific autoimmunity. Arch. Neurol. 65, 78–83.

Qin, K., Wu, W., Huang, Y., et al., 2017. Anti-N-methyl-D-aspartate receptor(NMDAR) antibody encephalitis presents in atypical types and coexists with neuromyelitis optica spectrum disorder or neurosyphilis. BMC Neurol. 17, 1.

Ramanathan, S., Dale, R.C., Brilot, F., 2016. Anti-MOG antibody: the history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination. Autoimmun. Rev. 15, 307–324.

Ran, Y., Wang, L., Zhang, F., Ao, R., Dong, Z., Yu, S., 2017. Anti-NMDAR encephalitis followed by seropositive neuromyelitis optica spectrum disorder: a case report and literature review. Clin. Neurol. Neurosurg. 155, 75–82.

Sato, D.K., Callegaro, D., Lana-Peixoto, M.A., et al., 2014. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. Neurology 82, 474–481.

Siritho, S., Sato, D.K., Kaneko, K., Fujihara, K., Prayoonwiwat, N., 2016. The clinical spectrum associated with myelin oligodendrocyte glycoprotein antibodies (anti-MOG-Ab) in Thai patients. Mult. Scler. 22, 964–968.

Titulaer, M.J., Hoftberger, R., Iizuka, T., et al., 2014. Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. Ann. Neurol. 75, 411–428.

Titulaer, M.J., McCracken, L., Gabilondo, I., et al., 2013. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 12, 157–165.

Wang, J.J., Jaunmuktane, Z., Mummery, C., Brandner, S., Leary, S., Trip, S.A., 2016. Inflammatory demyelination without astrocyte loss in MOG antibody-positive NMOSD. Neurology 87, 229–231.

Watanabe, M., Kondo, T., Murakata, K., et al., 2014. Antibodies to neural and non-neural autoantigens in Japanese patients with CNS demyelinating disorders. J. Neuroimmunol. 274, 155–160.

Wingerchuk, D.M., Banwell, B., Bennett, J.L., et al., 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85, 177–189.

Xu, Y., Wang, Q., Ren, H.T., et al., 2016. Comparison of efficacy and tolerability of azathioprine, mycophenolate mofetil, and cyclophosphamide among patients with neuromyelitis optica spectrum disorder: a prospective cohort study. J. Neurol. Sci. 370, 224–228.

Yokoyama, K., Hori, M., Yoshida, A., 2016. Anti-myelin oligodendrocyte glycoprotein antibody neuritis optica following anti-NMDA receptor encephalitis. Pediatr. Int. 58, 953–954.

Zhou, L., Huang, Y., Li, H., et al., 2017. MOG-antibody associated demyelinating disease of the CNS: a clinical and pathological study in Chinese Han patients. J. Neuroimmunol. 305, 19–28.

Zoccarato, M., Saddi, M.V., Serra, G., et al., 2013. Aquaporin-4 antibody neuromyelitis optica following anti-NMDA receptor encephalitis. J. Neurol. 260, 3185–3187.