Observational Study

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Anti-NMDA receptor encephalitis concomitant with myelin oligodendrocyte glycoprotein antibody diseases

A retrospective observational study

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Abstract

Anti-N-methyl-D-aspartate receptor encephalitis (NMDARe) can coexist with myelin oligodendrocyte glycoprotein antibody (MOG-ab) disease.

To characterize MOG-ab disease during NMDARe, we analyzed all the patients with MOG-ab disease and NMDARe from our hospital from December 2018 to December 2019 and data from a systematical review of previously published reports. Details of the patients identified were summarized and literature was reviewed.

Four of thirty (14.2%) patients with anti-NMDARe had overlapping MOG-ab disease in our department. Analyze together with previously reported cases. Thirty-two NMDARe patients had overlapping MOG-ab disease. The onset age ranged from 3 to 48 years. Twenty-four patients (74%) developed abnormal behavior or cognitive dysfunction during the episodes of anti-NMDARe. None of these patients had tumors. 84% (27/32) patients received high doses of steroids as first-line immunotherapy and 28% (9/32) received mycophenolate mofetil (MMF) to prevent relapse. Twenty-six of twenty-seven (96%) had a good outcome.

Steroids are the most common first-line immunotherapies in NMDARe overlapping MOG-ab disease. Most of the NMDARe patients overlapping MOG-ab disease have a good prognosis.

Abbreviations: AMPAR = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, AQP4 = aquaporin 4, CASPR2 = contactin-associated protein-like 2 receptor, CNS = central nervous system, CSF = cerebrospinal fluid, DPPX = dipeptide-peptidase like protein 6, GABABR = γ-aminobutyric acid-B receptor, HSE = Herpes simplex encephalitis, LGI1 = leucine-richglioma-inactivated protein 1, MOG-ab = myelin oligodendrocyte glycoprotein antibody, NMDAR-ab = NMDAR antibody, NMDARe = anti-N-methyl-D-aspartate receptor encephalitis, NMOSD = neuromyelitis optical spectrum disorder, ON = optic neuritis.

Keywords: anti-N-methyl-D-aspartate receptor encephalitis, myelin oligodendrocyte glycoprotein

1. Introduction

Anti-N-methyl-D-aspartate receptor encephalitis (NMDARe) is a well-characterized immune-mediated encephalitis induced by the presence of IgG autoantibodies directed against the GluN1 subunit of the NMDAR [NMDAR antibody (NMDAR-ab)] in cerebrospinal fluid (CSF) and/or serum and predominantly affects young women.[1] Characteristic clinical features of NMDARe include psychiatric symptoms, seizures, dyskinesias, movement disorders, memory dysfunction, speech disorders, decreased levels of consciousness, autonomic dysfunctions, and

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central hypoventilation.[1,2] NMDAR are membrane receptors widely expressed in the central nervous system on various cells such as neurons, oligodendrocytes but also astrocytes.[3] An overlap has been recognized in NMDARe and demyelinating diseases, such as acute disseminated demyelinating encephalomyelitis,[4] myelitis,[5,6] neuromyelitis optical spectrum disorder (NMOSD),[3,7–11] optic neuritis (ON),[12,13] and multiple sclerosis.[3,14–18] Some of the patients have demyelinating-like lesions which are usually transient.[2]

Myelin oligodendrocyte glycoprotein (MOG) is a membrane protein expressed on the surface of oligodendrocyte cell and myelin sheaths.[19] Recently, myelin oligodendrocyte glycoprotein antibody (MOG-ab) has been found in a subset of patients with NMOSD who are seronegative for aquaporin4-ab (AQP4-ab).[20,21] MOG-ab is now becoming a potential biomarker of inflammatory diseases of the central nervous system (CNS). It is associated with wider clinical phenotypes, not merely limited to NMOSD, but also with ON, encephalitis with brain demyelinating lesions, and/or myelitis.[22] In the current study, we aimed to further characterize the clinical features of MOG-ab diseases overlapping NMDARe and review literature.

2. Methods

2.1. Study subjects

In this retrospective observational study, we reviewed the patients from our department diagnosed as NMDARe overlapping MOG-ab disease from December 2012 to December 2019. Written consent was obtained from all the patients and the study was approved by the Ethics Committee of Beijing Tiantan Hospital affiliated with Capital Medical University (Beijing, China).

2.2. AQP4-ab, MOG-ab, and anti-NMDAR-ab detection

AQP4-ab and MOG-ab were detected by using indirect immunofluorescence on a commercial assay (Euro-immune) according to the manufacturer's instructions. CSF and serum NMDAR (GluN1 subunit), leucine-richglioma-inactivated protein 1 LGI1, contactin-associated protein-like 2 receptor (CASPR2), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), dipeptide-peptidase like protein 6 (DPPX), and γ-aminobutyric acid-B receptor (GABABR) antibodies were also examined using cell-based assays (Euro-immune).

2.3. Literature review

We searched PubMed through December 2019 for articles published in the English language with the search string ("Receptors, N-Methyl-D-Aspartate" [Mesh Terms]) AND ("Myelin Oligodendrocyte Glycoprotein" [Mesh Terms] OR "MOG" OR "Demyelinating Diseases" [MeSH Terms] OR "Demyelinating Autoimmune Diseases, CNS" [MeSH Terms]). We also searched the references for related published articles. All obtained articles were reviewed to identify the cases of overlapping MOG-ab disease and NMDARe.

3. Results

3.1. Results from our cases

Five of thirty (14%) NMDARe patients coexist with demyelinating disorders. Of them, 2 were males, 3 were females. MOG-ab was positive in 4 of the 5 patients. No patients were positive for the GABABR, AMPAR, CASPR2, LGI1, and DPPX antibodies. All of the 4 patients fulfilled the diagnostic criteria for definite NMDARe and we diagnosed the NMDARe mainly depending on the CSF NMDAR-ab. The onset age ranged from 25 to 48 years. No signs of malignancy were detected on extensive exploration with serum tumor markers, ultrasound, CT, and magnetic resonance imaging (MRI) in the 4 patients. Brain and spinal cord MRIs were performed in all our patients (Figs. 1–4). NMDARe occurred prior to the episode of MOG-ab disease in 2 patients (cases 1 and 2, 4–70 months), simultaneously in 1 patient (case 4), and after the episode of MOG-ab disease in 1 patient (case 3, 2 months).

All 4 patients had supratentorial and infratentorial lesions. Two of the 4 patients had spinal cord lesions (cases 1 and 2). Tables 1 and 2 summarize the demographic data and laboratory data of our 4 patients, respectively. MRI findings of the 4 patients were described in Figures 1–4, respectively. High doses of steroids were the main treatment for attacks in our patients.

3.1.1. Patient 1. A 25-year-old male complained of somnolent, behavioral, and psychiatric dysfunction for 1 month, seizures, and reduced level of consciousness for 12 days. He had presented with fever before admission. Brain MRI showed multiple T2-hyperintense lesions in bilateral frontal-parietal lobes, cingulate gyrus, and corpus callosum, some of which showed contrast enhancement (Fig. 1A). Lumbar puncture showed pleocytosis (18×10^6/L) and elevated protein level (22.41 mg/dL). The tests for AQP4-ab and MOG-ab were negative in his serum. Anti-NMDAR-ab (IgG isotype) titer was 1:32 in CSF and 1:100 in serum. At the same time, orofacial involuntary movements were noted. His symptoms were improved by intravenous dexamethasone (20 mg/day) and 5 days of intravenous immunoglobulin (IVIG) regimen (0.4 g/kg/day). A second MRI performed after 20 days of treatment indicated resolved lesions of the above-mentioned cortex (Fig. 1B). After discharge, he started on prednisone orally and titrated to 5 mg/day.

Four months later, he developed numbness and weakness in his right arm extremities. The numbness gradually progressed to his right arm, shoulder, chest, lower limb, and then left upper limb. Cranial MRI revealed T2-hyperintense lesions extending from the pontomedullary junction to C4 accompanied by spinal cord swelling and some contrast enhancement (Fig. 1C). The test for AQP4-ab was negative, but MOG-ab was positive in CSF (1:32). On day 12 after admission, the patient complained of itching from the face to the upper limbs. Five-day intravenously administered immunoglobulin was given without any improvement. His symptoms resolved 2 weeks after methylprednisolone (1000 mg/day) delivered intravenously and a tapering course of oral prednisolone. He was also treated with mycophenolate mofetil (MMF) and remained free of relapse.

3.1.2. Patient 2. A 48-year-old woman presented initially with a 70-day history of behavioral and psychiatric disorder (illusion, impulse, nonsense, self-harm). Ten days later, she developed vision loss in the right eye, paralysis, urinary retention, and sensory disturbance of the bilateral lower limbs. He had a history of a psychiatric disorder for 20 years. Brain MRI disclosed T2-hyperintense lesions in the pos without gadolinium (Gd) enhancement. Cranial and thoracic MRI showed T2-hyperintense lesions at C5–6, T1, T3, T5, T10–12 with Gd enhancement (Fig. 2A). The tests for AQP4-ab and MOG-ab were negative in serum and CSF. Anti-NMDAR-abs were positive in CSF (titer 1:100) and negative in serum. Besides, serum antinuclear antigen

Table 1

Demographic, clinical, and neuroimaging findings in our 4 patients of NMDARe overlapping MOG-ab disease.

Case no.	Sex, age	Ep. no.	Clinical syndrome	Interval mo.	Presenting manifestations	MRI findings	Immunotherapy	mRS max	mRS after Ep.
1	M, 25	1	NMDARe	4	Sleep disorder, behavioral, and psychiatric dysfunction, seizures	Multiple T2-hyperintense in bilateral frontal-parietal lobes, cingulate gyrus, and corpus callosum with contrast-enhancing lesions	Short-term DEXA, IVIG, oral st taper	–	–
		2	MOG-ab disease		LETM	T2-hyperintense lesions extending from the pontomedullary junction throughout the cervical cord to C4	High-dose IVMP, IVIG, oral st taper	3	2
2	F, 48	1	NMDARe	2.6	Behavioral and psychiatric disorder	n.d.	High-dose IVMP, IVIG, oral st taper	–	–
		2	MOG-ab disease		ON, paralysis, and sensory disturbance of the bilateral lower limbs	1st DSE: T2-hyperintense lesions in the pos, cranial and thoracic MRI showed T2-hyperintense lesions at C5–6, T1, T3, T5, T10–12 with Gd enhancement	High-dose IVMP, oral st taper	5	4
						2nd DSE: T2-hyperintense lesions in the right frontal lobe, cerebellum, and the left medulla. Cranial and thoracic MRIs showed T2-hyperintense lesions in C3–T1 and T3–T6	High-dose IVMP, oral st taper, RTX	5	4
3	F, 37	1	MOG-ab disease	2	Droopy eyelids in the left eye and double vision	T2-hyperintense signals in the left middle cerebral brain, cerebrum and thalamus with meninges enhancement	High-dose IVMP, oral st taper	2	1
		2	NMDARe		Seizures	T2 lesions within left cerebellum, left temporal cortex, left anterior horn of ventricle without Gd enhancement	High-dose IVMP, IVIG, oral st taper, MMF	5	1
4	M, 21	1	MOG-ab disease and NMDARe	0	Headache, fever, seizures, and ON	Shallowness of the right frontal temporal lobe sulcus with contrast enhancement of the meninges	High-dose IVMP	2	0

DEXA = dexamethasone, Ep. = episode, F = female, IVIG = intravenous immunoglobulins, IVMP = intravenous injection of methylprednisolone, LETM = longitudinally extensive transverse myelitis, M = male, MMF = mycophenolate mofetil, MOG-ab = myelin oligodendrocyte glycoprotein antibody, MRI = magnetic resonance imaging, mRS = modified Rankin scale, NMDARe = anti-N-methyl-D-aspartate receptor encephalitis, no. = number, ON = optic neuritis, RTX = rituximab, st = steroids.

antibodies were positive, with a titer of 1:320. The patient's condition deteriorated despite the use of IVIG and high-dose pulse IV methylprednisolone (IVMP). Lumbar MRI showed long T1 and long T2 signals in spinal conus with Gd enhancement (Fig. 2B). Cranial showed T2-hyperintense lesions between C3 and T3 with Gd enhancement (Fig. 2C). Given that the patient only used hormones for 3 days, we retain the same treatment. Thereafter, her symptoms relieved gradually. However, the test for anti-NMDAR-ab became negative and MOG-IgG became positive in CSF after discharge.

Table 2

Laboratory findings in our patients.

Case no.	Sex, age	Ep. no.	Clinical syndrome	Tumor	Neuronal autoantibodies	SOB	AQP4-ab (CSF/serum)	MOG-ab (CSF/serum)	NMDAR-ab (CSF/serum)
1	M, 25	1	NMDARe	Negative	Negative	Negative	n.d.	n.d.	Positive (1:100)/positive (1:32)
		2	MOG-ab	n.d.	n.d.	Negative	Negative/negative	Negative/positive (1:32)	n.d.
2	F, 48	1	NMDARe	n.a.	Negative	n.a.	n.a.	n.a.	n.a.
		2	MOG-ab	Negative	n.d.	Negative	Negative/negative	Negative/negative	Positive (1:100)/negative
		3	MOG-ab	n.d.	n.d.	Negative	n.d.	Positive (1:32)/negative	Negative/negative
3	F, 37	1	MOG-ab	Negative	n.d.	Positive	Negative/negative	Positive (1:32)/negative	n.d.
		2	NMDARe	Negative	Negative	Negative	n.d.	n.d.	Positive (1:10)/positive (1:100)
4	M, 29	1	NMDARe and MOG-ab	Negative	Negative	Negative	Negative/negative	Negative/positive (1:32)	Positive /positive

ab = antibody, AQP4 = aquaporin-4, CSF = cerebrospinal fluid, Ep. = episode, MOG = myelin oligodendrocyte glycoprotein, n.a. = not applicable, n.d. = not done, NMDARe = N-methyl aspartate receptor encephalitis, no. = number, SOB = specific oligoclonal band.

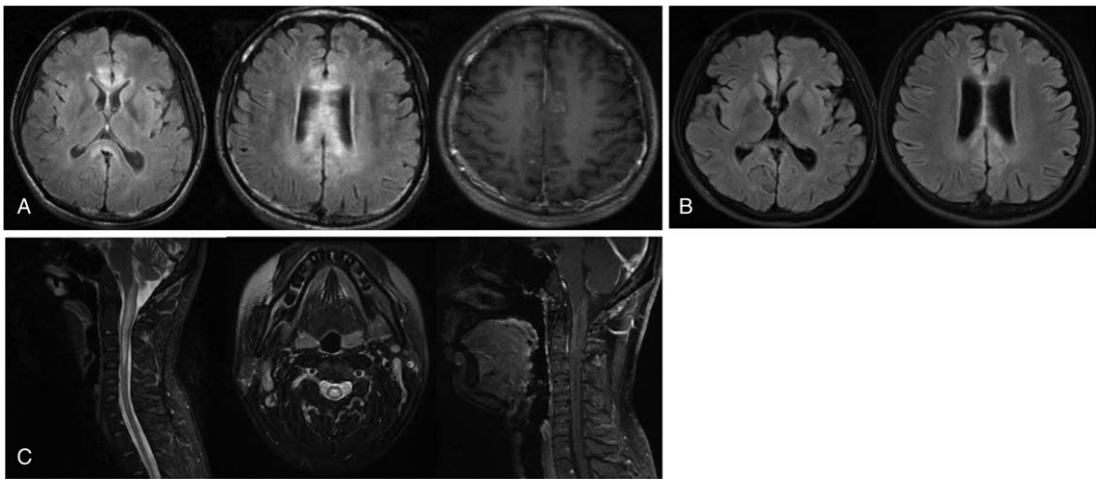

Figure 1. Brain MRI (sagittal T2 FLAIR images) showed high signal in the white matter and peri-ventricular with contrast-enhancing lesions at T1 (A). Brain MRI showed a high signal reduced after immunotherapy (B). MRI of the cervical cord showed T2 hyperintensities from the dorsal medulla to C4, including contrast-enhancing lesions (C).

Four months later, she exhibited lower limb weakness and dysuria, and the symptoms gradually aggravated with intermittent cognitive impairment and gibberish. Repeat cranial and thoracic MRIs showed T2-hyperintense lesions in C3-T1 and T3-T6 (not shown). She received IVMP only and relapsed 6 months later with bilateral lower extremity weakness, decreased binocular vision, and abnormal mental behavior (intermittent unfamiliarity with relatives, gibberish, mood fluctuations). Brain MRI showed T2-hyperintense lesions on the brain with non-contrast enhancement (Fig. 2D). Rituximab was administered. After a 21-day hospitalization, the paraparesis improved significantly. So far, no recurrence has been found.

3.1.3. Patient 3. A 37-year-old female manifested droopy eyelids in the left eye and double vision. MRI follow-up showed T2-hyperintense signals in the left middle cerebral brain, cerebrum, and thalamus with meninges enhancement. Her CSF demonstrated an increase in white blood cell numbers (158/mm^3), mainly mononuclear cells. Protein was 0.51 mg/dL. MOG-ab was positive in CSF. After treatment with methylprednisolone (500 mg per day intravenously for 5 days), ceftriaxone (2 g intravenously) and aciclovir (750 mg, 3 times per day intravenously), her symptoms improved.

About 2 months later, she developed daily headaches and 1 generalized seizure. Brain MRI showed T2 lesions within the left cerebellum, left temporal cortex, left anterior horn of ventricle without contrast (Fig. 3). On day 15 of admission, the patient experienced shouting, gibberish, and 1 generalized seizure. The NMDAR-ab was found in both CSF (titer: 1:10) and serum (titer:

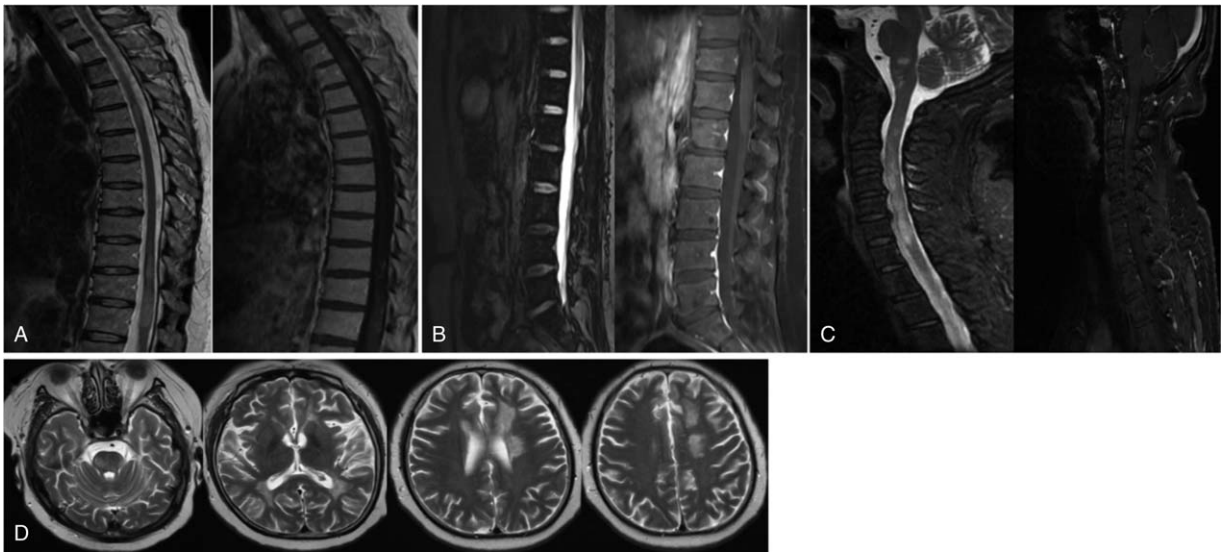

Figure 2. Thoracic MRI showed an extension of T2 lesions in T1, T3, T5, T10–12 with gadolinium (Gd) enhancement (A). Lumbar MRI showed long T1 long T2 signal in spinal conus with Gd enhancement (B). MR FLAIR imaging demonstrated multiple hyperintense lesions. Several lesions were found to be Gd enhancing on T1 (C). Brain MRI showed multiple hyperintense T2 lesions on the brain stem, bilateral ventricles, the left corona radiata, the centrum semiovale, and the white matter bilateral frontal with non-contrast enhancement (D).

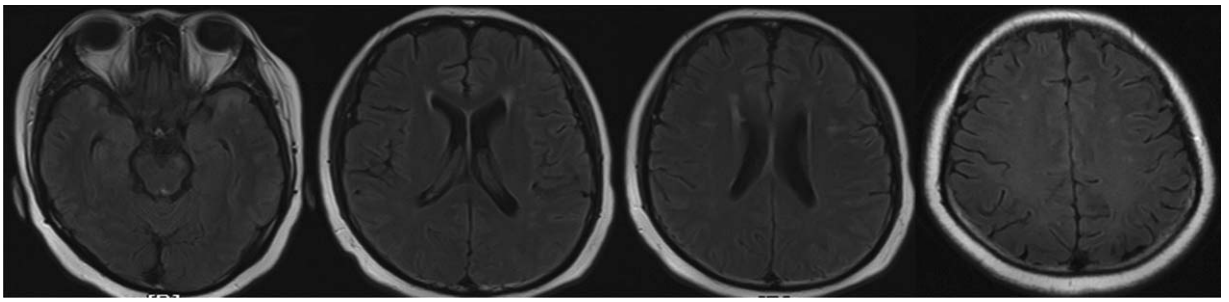

Figure 3. Brain MRI showing T2 lesions in the left cerebellum, bilateral temporal lobe, frontal lobe, lateral ventricles, and center of semioval without Gd enhancement.

1:100). As soon as anti-NMDAR-ab was detected, she received IVIG and IVIP followed by a weaning course of oral prednisolone. Steroid-pulse therapy ameliorated her symptoms. To prevent relapse, we also gave her MMF.

3.1.4. Patient 4. A 21-year-old male presented with headache, fever, and generalized seizures. Initial MRI revealed the shallowness of the right frontal temporal lobe sulcus with contrast enhancement of the meninges (Fig. 4). His serum and CSF were tested for NMDAR-abs; the CSF was positive (1:32). We initially thought it was viral meningoencephalitis. After treatment with aciclovir and anti-epileptic for 15 days, the patient complained of a loss of vision in the right eye and could only see the fingers moving 1 m in front of his eyes. Orbital MRI showed T2 hyperintensities within the anterior of the bilateral optic nerve (Fig. 4). Repeat CSF analysis showed serum AQP4-ab was negative, while MOG-ab was positive (1:32). Anti-NMDAR-ab was weakly positive in CSF. Visual evoked potentials and EEG are normal. His symptoms improved following IVMP, IVIG, and a tapering course of oral prednisolone. In subsequent MRI studies, these lesions were no longer observed.

Three months later, the patient had another seizure. No lesions were found in brain MRI. Muscle biopsy and mitochondrial gene screening were negative, which excluded the possibility of metabolic encephalopathy and mitochondrial encephalopathy. This led us to consider the possibility of anti-NMDARe in our patient.

3.2. Results from a literature review

The initial literature search yielded 143 published reports. We reviewed the reports and their references for related published reports and identified other patients with MOG-ab disease. One case was excluded because the symptoms of anti-NMDARe were absent, although anti-NMDAR-ab was positive.

Of 30 patients with anti-NMDARe and MOG-ab disease (excluding 2 patients with unknown information), 12 anti-NMDARe patients occurred concurrently with MOG-ab disease, 14 preceded and 4 followed by independent episodes of MOG-ab disease. The onset age of these 32 patients ranged from 3 to 48 years. Twenty-four patients (74%) developed abnormal behavior or cognitive dysfunction during the episodes of anti-NMDARe. Abnormal behavior or cognitive dysfunction was the most common manifestation during attacks associated with anti-NMDARe in the above-mentioned 3 conditions, and brainstem demyelination was the most common onset manifestations of MOG-ab disease when anti-NMDARe occurred concurrently or preceded with MOG-ab disease (50%, 42%, respectively). None of the 32 patients had tumors. 84% (27/32) patients received high doses of steroids as first-line immunotherapy and 28% (9/32) received MMF to prevent relapse. Twenty-six of twenty-seven (96%) had a good outcome. The characteristics of these previously reported patients along with our 4 patients are summarized in Tables 3 and 4.

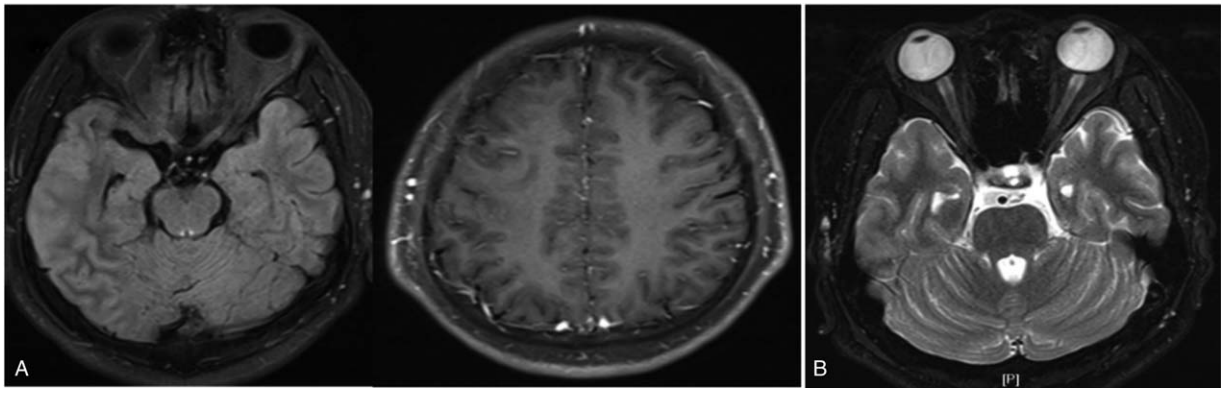

Figure 4. Brain MRI revealed the shallowness of the right frontal temporal lobe sulcus with contrast enhancement of the meninges (A) and orbital MRI showed T2 hyperintensities within the anterior of the bilateral optic nerve (B).

Table 3

The characteristics of MOG-ab overlapping anti-NMDARe from these previously reported patients along with our 4 patients.

Characteristics	MOG-ab overlapping anti-NMDARe (n = 32)
Age at onset, (range), y	3–48[*]
≤14 (pediatric patients), n (%)	7 (21%)
Sex (female), n (%)	12 (38%)
First episode, n (%)[*]	
Anti-NMDARe	14 (47%)
MOG-ab	4 (13%)
MOG-ab and anti-NMDARe	12 (40%)
Symptoms of anti-NMDARe, n (%)[†]	
Abnormal behavior or cognitive dysfunction	24 (77%)
Seizure	10 (32%)
Speech dysfunction	11 (35%)
Decreased level of consciousness	14 (45%)
Movement disorder, dyskinesia, or rigidity posture	13 (42%)
Autonomic dysfunction or central hypoventilation	5 (16%)
Optic neuritis, n (%)	10 (31%)
No. (%) with the following lesions detected by MRI	
Supratentorial lesion	27 (84%)
Infratentorial lesion	11 (34%)
Spinal cord lesions	7 (22%)
Tumor, n (%)	0[‡]
Treatment, n (%)	
Steroids	27 (84%)
IVIG	13 (48%)[§]
PLEX	1 (3%)
MMF	9 (28%)
RTX	4 (13%)
AZA	3 (9%)
IFN-beta	2 (6%)
Natalizumab	1 (3%)
CTX	1 (3%)
Favorable outcome, last mRS (0–2), n (%)	26 (96%)[§]

ab = antibody, AZA = acetazolamide, CTX = cyclophosphamide, IFN = interferon, IVIG = intravenous immunoglobin, MMF = mycophenolate mofetil, MOG = myelin oligodendrocyte glycoprotein, MRI = magnetic resonance imaging, mRS = modified Rankin scale, n = number, NMDARe = N-methyl-D-aspartate receptor encephalitis, PLEX = plasma exchange, RTX = rituximab, y = year.

[*] 2 patients unknown.

[†] 1 patient unknown.

[‡] 11 patients unknown.

[§] 5 patients unknown.

4. Discussion

Anti-NMDARe is the most common autoimmune encephalitis of the limbic system.[1] It is now recognized that the range of anti-NMDAR encephalitis is wider, as there are many cases in women, men, and children.[2,3] 33% of patients with anti-NMDARe have mild, or transient abnormal brain MRI[9] and the lesions can occur in the hippocampi, corpus callosum, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem, and the spinal cord.[1,2] The MOG-ab disease is an inflammatory demyelinating syndrome of CNS. When the clinical manifestations of the 2 overlap, especially when the brain stem is involved, it is extremely difficult to identify.[24,25]

There are few reports on the overlap of MOG antibodies and NMDAR antibodies. Titulaer et al[3] firstly reported that 23 of 691 patients with anti-NMDAR encephalitis have a demyelinating disorder and most had AQP4-IgG or MOG-IgG antibodies. Thereafter, cases of anti-NMDARe combined with MOG-ab disease have been reported.[13,25–30] According to these previously reported patients and our 4 patients, we found that the clinical manifestations of the overlap of these 2 syndromes may have the following characteristics:

(1) Consistent with previous studies,[3,25,28,30] symptoms of anti-NMDARe and MOG-ab disease exist independently or overlap sometimes.
(2) Abnormal behavior or cognitive dysfunction is both the most common and the most common initial symptoms during attacks associated with anti-NMDARe, and brain demyelination was the most common initial manifestations of MOG-ab disease.
(3) High-dose steroids were the most commonly used first-line immunotherapy.
(4) No tumors were detected in these patients, and most patients demonstrated good recoveries, this is in line with previously reported cases.[12,31]

Viral studies for influenza viruses B IgM were positive in patient 1. We think influenza B viruses may be an infectious etiology. A study by the California Encephalitis Project found that the frequency of anti-NMDARe surpassed that of any individual viral etiology in young individuals.[32] Nakamura et al[33] described MOG-IgG-positive ADEM after infectious mononucleosis and Amano et al[34] reported MOG-IgG-positive longitudinally extensive transverse myelitis after influenza infection. Herpes simplex encephalitis (HSE) has been reported as a possible trigger of NMDAR-ab formation.[35–39] Whether this infectious entity is caused by molecular mimicry or breakdown of immunologic tolerance towards the NMDAR expressed by damaged neurons in an inflamed environment is unknown. Synthesis of NMDAR-ab may begin after HSE.[35] However, CSF PCR assays for viral pathogens [HSV-1, HSV-2, HSV (1 + 2)] were all negative in our patients. There is also a possibility that pregnancy and/or delivery could trigger anti-NMDAR encephalitis, as several patients developed this disorder during pregnancy or in the postpartum period.[40–42] However, none of our patients suffer from this condition.

Several retinal neurons express NMDAR and might be affected directly in acute anti-NMDARe; however, the retinal structure appears unaltered in those acute anti-NMDARe who have mild visual dysfunction in these patients.[43] Patient 4 presented with decreased vision. Since visual dysfunction is not among the common symptoms of acute NMDARe.[43] Our hypothesis was ON as the first event of demyelinating disorders. Interestingly, MOG-ab was positive in CSF. Optical coherence tomography revealed an increase in the thickness of the binocular retinal nerve fibre layer in the right eye. These confirmed our diagnosis.

Autoantibodies against NMDAR might be closely related to clustered seizures. Seizures can occur at any time during the disease. MOG-ab disease has also been recently described in association with seizures.[44] As in our study, 3 of 32 patients presented with onset seizures during MOG-ab disease. Hamid et al reported that patients with MOG-IgG antibodies were more likely to have seizures or an encephalitis-like illness than AQP4-IgG-positive NMOSD patients.[19] Nabbout et al[45] reported that some epilepsy patients who are not sensitive to routine anticonvulsants may have immune-mediated causes. The contribution of NMDAR-abs and other antibodies (such as AQP4, MOG) to demyelination is unknown, but it is noteworthy that oligodendrocytes express NMDAR,[46] and that the immune attack targeting myelin may simultaneously involve NMDAR and vice versa.

Table 4

The symptoms at onset of anti-NMDARe coexisting with MOG-ab disease from these previously reported patients along with our 4 patients.

	Anti-NMDAR (n = 14)		MOG-ab (n = 4)		
	Anti-NMDARe	MOG-ab	Anti-NMDARe	MOG-ab	MOG-ab overlapping anti-NMDARe (n = 12)
Symptoms at onset of anti-NMDARe, n(%)					
Abnormal behavior or cognitive dysfunction	9 (64%)	–	2 (67%)*	–	9 (75%)
Seizure	4 (29%)	–	0	–	5 (42%)
Speech dysfunction	4 (29%)	–	1 (33%)*	–	3 (25%)
Decreased level of consciousness	5 (36%)	–	0	–	4 (33%)
Movement disorder, dyskinesia or rigidity posture	4 (29%)	–	0	–	1 (8%)
Autonomic dysfunction or central hypoventilation	1 (7%)	–	0	–	1 (8%)
Symptoms at onset of MOG-ab, n(%)					
Seizure	–	1 (7%)	–	1 (25%)	1 (8%)
ON	–	5 (36%)	–	2 (50%)	1 (8%)
Myelitis	–	3 (36%)	–	0	2 (17%)
ON + myelitis	–	0	–	0	0
Brainstem	–	7 (50%)	–	0	5 (42%)
Cerebellum	–	1 (7%)	–	0	3 (25%)
Brain	–	6 (43%)	–	2 (50%)	4 (33%)
ON + brain	–	2 (14%)	–	0	0

ab = antibody, MOG = myelin oligodendrocyte glycoprotein, n = number, NMDARe = N-methyl-D-aspartate receptor encephalitis, ON = optic neuritis.
* 2 patients unknown.

There are some limitations to our study. First, the number of reported cases available for evaluation is small. Second, the retrospective study is also a limitation. Finally, detection methods of MOG-ab are not uniform in each literature.

5. Conclusions

The results of these case studies suggest that patients with anti-NMDARe may develop concurrent or separate episodes of MOG-ab disorders. Anti-NMDARe patients with atypical episodes (especially ON or myelitis) or brain demyelination (especially brainstem) may have MOG-ab disease, and MOG-ab disease with unusual symptoms (such as psychiatric manifestations or cognitive dysfunction, decreased level of consciousness, seizure) may have anti-NMDARe. The tests for anti-NMDAR-ab and MOG-ab should be considered in these patients. Early diagnosis and treatment can improve the patient's outcome.

Author contributions

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