Neuromyelitis optica spectrum disorders with non-opticospinal manifestations as initial symptoms: A long-term observational study

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Abstract

Background

Early stage neuromyelitis optica spectrum disorders (NMOSD) with non-opticospinal manifestations as initial symptoms are easily misdiagnosed; however, data on the full symptom profile are limited. Moreover, the clinical characteristics and long-term outcomes of these patients remain unknown. We sought to analyze the clinical characteristics, imaging features, and long-term outcomes of NMOSD with non-opticospinal manifestations as initial symptoms.

Methods

We retrospectively included relevant patients from our center. Clinical, demographic, magnetic resonance imaging (MRI), treatment, and outcome data were compared according to the non-opticospinal vs. opticospinal initial symptoms.

Results

We identified 43 (9.13%) patients with non-opticospinal initial symptoms among 471 patients with NMOSD. Of these, 88.37% developed optic neuritis/myelitis during an average follow-up of 6.33 years. All non-opticospinal symptoms were brain/brainstem symptoms. Most symptoms and associated brain lesions were reversible. These patients had a younger onset age ($P < 0.001$), lower serum aquaporin-4 (AQP4) antibody titers ($P = 0.030$), and Expanded Disability Status Scale (EDSS) score was lower at onset ($P < 0.001$) and follow-up ($P = 0.041$) than NMOSD patients with opticospinal initial symptoms. In addition, EDSS scores reached 3.0 (indicating moderate disability) later than in patients with opticospinal initial symptoms ($P = 0.028$).

Conclusions

Patients with NMOSD with non-opticospinal initial symptoms have a younger onset age, lower serum AQP4 antibody titers, and better clinical outcomes.

1. Introduction

Neuromyelitis optica (NMO) was first described by Devic and Gault over a century ago as a monophasic disorder characterized by bilateral optic neuritis (ON) and myelitis (MY).[1, 2] The discovery of highly-specific anti-aquaporin-4 (AQP4) antibodies established NMO as a distinct disease,[3] which required the presence of ON and MY for diagnosis.[4] However, subsequently, more restricted or more extensive central nervous system (CNS) involvement in NMO has been recognized, and the term NMO spectrum disorders (NMOSD) was proposed to encompass the entire clinical spectrum in the international consensus diagnostic criteria in 2015.[5, 6] The new criteria define a unifying diagnosis of NMOSD, which requires at least 1 of 6 core clinical characteristics in patients who are seropositive for AQP4 antibodies. The core clinical characteristics include ON, MY, area postrema syndrome, acute brainstem syndrome, diencephalic syndrome, and symptomatic cerebral syndrome with typical brain lesions. The new criteria extend the clinical scope of NMOSD beyond ON and MY and thus demand a high index of clinical suspicion in patients who present with non-opticospinal CNS manifestations. NMOSD with non-opticospinal manifestations as initial symptoms (NOSIS) are easily misdiagnosed in the early stage of the disease, and data on the full profile of NOSIS in NMOSD are limited. Moreover, the clinical characteristics and long-term clinical outcomes of patients with NMOSD with NOSIS (NMOSD-NOSIS) remain unknown.

Here, we describe the clinical characteristics and long-term clinical outcomes of patients with NMOSD-NOSIS. This study may provide insight into the disease pathogenesis and facilitate the early recognition of NMOSD.

2. Methods

2.1. Case selection and identification

Patients admitted to the Department of Neurology of The Third Affiliated Hospital of Sun Yat-Sen University between January 2013 and June 2019 were included if they fulfilled the Wingerchuk NMO diagnostic criteria; patients who met the Wingerchuk 2006 criteria were reconfirmed based on the 2015 report.[4, 6] Patients with an uncertain AQP4-IgG status, disease duration < 12 months, insufficient information, or a history of other CNS diseases were excluded. Patients included in the study were divided into two groups: NMOSD-NOSIS and NMOSD with opticospinal manifestations as initial symptoms (NMOSD-OSIS). In addition, all subjects must have had at least one follow-up visit at our center more than 1 year after the onset of symptoms. Fulfillment of the inclusion and exclusion criteria was confirmed retrospectively by a review of medical records by two neurologists specialized in the demyelinating diseases (Yuge Wang and Wei Qiu).

2.2. Standard protocol approvals, registrations, and patient consents

The Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University approved this study. Written informed consent was obtained from each patient.

2.3. Clinical data

The patients' medical records were reviewed retrospectively, and the following data were retrieved: sex, age at onset, disease duration (from the onset of disease to the most recent visit), annual relapse rate (ARR), coexisting autoimmune diseases, Expanded Disability Status Scale (EDSS) at onset and at the most recent visit, clinical manifestations, laboratory and MRI findings, and therapy including use of azathioprine, mycophenolate mofetil, and rituxmab. A relapse was defined as a new neurological deficit that lasted for > 24 hours and occurred > 30 days after the previous episode.[7] To analyze the frequencies of different relapses, we defined the following relapse phenotypes: isolated ON, isolated MY, simultaneous or sequential ON and MY occurring within 4 weeks, with or without brain/brainstem symptoms (ON + MY), isolated brain/brainstem presentations (brain/brainstem), and others (e.g., ON + brain/brainstem presentation, MY + brain/brainstem presentation, etc.).

2.4. Laboratory tests

Systemic disease diagnostic tests were routinely performed in most cases, including screening for anti-Ro/SSA and anti-La/SSB antibodies, anti-nuclear antibody, anti-double-stranded DNA antibody, anti-Smith antibody, anti-U1RNP antibody, anti-neutrophil cytoplasmic antibody, and rheumatoid factor. Serum AQP4 antibodies were tested using aquaporin 4-transfected cells from a commercial sampling kit (EUROIMMUN AG, Lübeck, Germany) according to the manufacturer's instructions.

2.5. MRI scanning

MRI scans of brain and spinal cord were performed on a GE 3.0 T MR imager scanner (General Electric, Milwaukee, WI) or a GE 1.5 T MR imager scanner (General Electric, Milwaukee, WI), in the Radiology Department of the Third Affiliated Hospital of Sun Yat-Sen University. The imaging parameters for 3.0 T MR included: T1 with and without gadolinium enhancement (1,780/24.5 ms, repetition time (TR)/echo time (TE)), T2 (5,600/90 ms, TR/TE), and fluid attenuated inversion recovery (8,400/150 ms, TR/TE) sequences. The imaging parameters for 1.5 T MR were as follows: T1 with and without gadolinium enhancement (400/15.5 ms, TR/TE), T2 (2,500–3,500/100 ms, TR/TE), and fluid attenuated inversion recovery (8,800/120 ms, TR/TE) sequences.

2.6. Statistical analysis

Statistical analyses were conducted using SPSS version 22.0 (SPSS, Chicago, IL, USA). The two-tailed *t*-test, Mann-Whitney U test, χ^2 test, and Fisher's exact test were used to compare the NMOSD-NOSIS and NMOSD-OSIS groups, and Wilcoxon's two-sample test was used to compare pre- and post-treatment annual relapse rates (ARRs). Time to reach an Expanded Disability Status Scale (EDSS) score of 3.0 in the NMOSD-NOSIS and NMOSD-OSIS groups was analyzed using Kaplan-Meier curves. A P value < 0.05 indicated statistical significance.

3. Results

3.1. Clinical characteristics and imaging features of patients with NMOSD-NOSIS

We identified 43 (9.13%) patients with NMOSD-NOSIS among 471 patients with NMOSD (Fig. 1). Table 1 summarizes the demographic and clinical features of the patients with NMOSD-NOSIS. Thirty-eight (88.37%) of these patients developed ON/MY

during the follow-up, while the other five patients showed only non-opticospinal manifestations during the follow-up period. The median time within which NMOSD-NOSIS patients developed ON/MY was 16.15 months (range: 2-187 months). The mean age at onset in the NMOSD-NOSIS cohort was 29.28 ± 11.36 years. The mean disease duration at last follow-up was 6.33 ± 5.06 years. Serum AQP4-IgG positivity rate was 83.72%. The disease duration of NMOSD-NOSIS patients who demonstrated only non-opticospinal manifestation during the follow-up period was shorter than that of NMOSD-NOSIS patients who developed ON/MY during the follow-up period (3.00 [1.00, 7.00] vs. 5.50 [2.00, 23.00], P = 0.043). There were no significant differences in other clinical manifestations and disabilities between the NMOSD-NOSIS patients who developed ON/MY and NMOSD-NOSIS patients who showed only non-opticospinal manifestations during the follow-up period (Table 1). Among these NMOSD-NOSIS cases, 15 patients with vomiting or hiccups as initial symptoms first visited the Department of Gastroenterology, one case with peripheral facial paralysis as initial symptom was first diagnosed with facial neuritis, while two cases with dysphagia and quadriplegia were first diagnosed with Guillain-Barre Syndrome (GBS). Eighty-one non-opticospinal initial symptoms in these 43 NMOSD-NOSIS patients were analyzed. The most common non-opticospinal initial symptom was vomiting (67.44%), followed by hiccups (44.19%), vertigo (16.28%), diplopia (16.28%), limb weakness/numbness (9.30%), dysphagia (6.98%), somnolence (4.65%), ataxia (4.65%), headache (4.65%), facial paralysis (4.65%), facial hypoesthesia (2.33%), limb spasm (2.33%), tinnitus (2.33%), and psychiatric symptoms (2.33%) (Fig. 2A). Fifty-seven non-opticospinal initial symptoms went untreated or were treated symptomatically, 24 non-opticospinal initial symptoms were treated with high-dose intravenous corticosteroid therapy. Most of these initial symptoms completely disappeared, even without steroid treatment in some cases. The total complete remission (CR) rate of these initial non-opticospinal symptoms was 66.67%, including a vomiting CR rate of 89.66% and a hiccup CR rate of 84.21% (Fig. 2B).

Table 1
Comparison about the demographic and clinical features between NMOSD-NOSIS patients with different developments.

	Total n = 43	NMOSD-NOSIS developing ON/MY n = 38	NMOSD-NOSIS restricted in non-ON/MY n = 5	P value
Age of onset, y	29.28 ± 11.36	29.05 ± 11.55	31.00 ± 0.89	0.723
Disease duration, y	5.00(1.00,23.00)	5.50(2.00,23.00)	3.00(1.00,7.00)	0.043
AQP4-IgG+, n(%)	36 (83.72)	32 (84.21)	4 (80.00)	0.811
ARR	0.75(0.14,4.00)	0.75(0.14,3.00)	0.67(0.29,4.00)	0.640
Coexisting autoimmunity, n(%)	6 (13.95)	5 (13.16)	1 (20.00)	0.592
CSF leukocyte cell count, n/ul	0.30(0,64.00)	3.00(0,64.00)	1.00(0,18.00)	0.942
CSF protein, mg/L	0.26 ± 0.13	0.26 ± 0.14	0.26 ± 0.11	0.980
EDSS at onset	0(0,9.50)	0(0,9.50)	2.00(0,2.00)	0.333
EDSS at follow-up	2.50(0,9.50)	2.75(0,9.00)	2.00(0,5.00)	0.616

NMOSD: neuromyelitis optica spectrum disorders; NMOSD-NOSIS: NMOSD with non-opticospinal manifestations as initial symptoms; NMOSD-OSIS: NMOSD with opticospinal manifestations as initial symptoms; ON:optic neurotis; MY:myelitis; AQP4: anti-aquaporin-4; ARR:annual relapse rate; CSF:cerebral spinal fluid; EDSS:expanded disability status scale.

To compare the difference of recovery of non-opticospinal symptoms and opticospinal symptoms, we selected all the isolated ON relapses (n = 21) and MY relapses (n = 25) in these 43 NMOSD-NOSIS patients as controls. We found that the CR rate of non-opticospinal symptoms was higher than that of opticospinal symptoms (Fig. 2B).

Brain MRI was not performed in two patients. Twelve patients with NMOSD with vomiting and hiccup as initial symptoms did not undergo brain MRI examination at the time of onset, and no obvious abnormality was found in brain MRI performed later, during the follow-up. Twenty-nine NMOSD-NOSIS patients underwent brain MRI examinations at the time of onset. The main responsible lesions for these symptoms were in the area postrema (68.42%), brainstem (other areas) (20.69%), brachium pontis (13.79%), brainstem (periependymal) (10.34%), diencephalon (10.34%), and cerebellum (3.45%) (Fig. 3A). Most of the lesions around the third/fourth ventricle disappeared during follow-up (disappearance rate of lesions: area postrema: 69.23%; diencephalon: 100%). The

further away from the third/fourth ventricle the lesion occurred, the less likely the lesions were to disappear (disappearance rate of lesions: periependymal areas in brainstem: 50%; other areas of the brainstem 66.67%; brachium pontis 0%; and cerebellum 0%) (Fig. 3B). In addition, five patients with vomiting and hiccups as initial symptoms had no obvious cerebral lesions in the brain MRI at the time of onset. One patient had a lesion in the area postrema of the medulla oblongata after 6 months.

3.2. Comparison of clinical characteristics, imaging features and long-term clinical outcomes between NMOSD-NOSIS and NMOSD-OSIS patients

To prevent the interference of antibody serotypes, we only compared the differences between the NMOSD-NOSIS and NMOSD-OSIS patients who were serum-positive for AQP4 antibodies. As shown in Table 2 and Fig. 4, NMOSD-NOSIS patients had a younger onset age (27.27 ± 10.08 years vs. 37.16 ± 14.28 years, $P < 0.001$) and lower serum AQP4 titers than NMOSD-OSIS patients (Log[serum AQP4 titers]: 1.59 ± 0.50 vs. 1.81 ± 0.48, $P = 0.030$) (Fig. 4A). The NMOSD-NOSIS patients had lower EDSS scores at onset and follow-up than the NMOSD-OSIS patients (EDSS at onset: 0 [0, 9.50] vs. 3.00 [0, 9.50], $P < 0.001$; EDSS at follow-up: 2.50 [0, 9.00] vs. 3.00 [0, 9.50], $P = 0.041$). Moreover, NMOSD-NOSIS patients reached an EDSS 3.0 later than NMOSD-OSIS patients (11.75 ± 1.76 years vs. 6.19 ± 0.48 years, $P = 0.028$) (Fig. 4B). After follow-up, there was no difference in the frequency of the ON + MY phenotype between the NMOSD-NOSIS patients and the NMOSD-OSIS patients (57.58% vs. 61.42%, $P = 0.664$). When analyzing all 1243 relapse episodes in the two groups, we observed that NMOSD-NOSIS patients had more frequent isolated brain/brainstem attacks during the disease course than did NMOSD-OSIS patients (12.40% vs. 3.11%, $P < 0.001$) (Table 2).

Table 2
Comparison about the clinical and imaging features between NMOSD-NOSIS and NMOSD-OSIS patients (serumpositive for AQP4)

	NMOSD-NOSIS n = 33	NMOSD-OSIS n = 381	P value
Age of onset, y	27.27 ± 10.08	37.16 ± 14.28	< 0.001
Disease duration, y	4.00(1.00,23.00)	5.00(1.00,30.00)	0.946
ARR	1.00(0.14,3.00)	0.70(0.07,3.00)	0.133
Coexisting autoimmunity, n(%)	3/33(9.09)	84/381(22.05)	0.080
EDSS at onset	0(0,9.50)	3.00(0,9.50)	< 0.001
EDSS at the last follow-up	2.50(0,9.00)	3.00(0,9.50)	0.041
Clinical phenotype			
ON	0/330(0)	43/381(11.29)	0.082
MY	0/33(0)	69/381(18.11)	0.007
ON + MY	19/33(57.58)	234/381(61.42)	0.664
Brain/brainstem	4/33(12.12)	0/381(0)	< 0.001
Others	10/33(30.30)	35/381(9.19)	0.001
Relapse phenotype			
ON	26/129(20.16)	333/1114(29.89)	0.021
MY	55/129(42.64)	496/1114(44.52)	0.683
ON + MY	15/129(11.63)	215/1114(19.30)	0.034
Brain/brainstem	16/129(12.40)	38/1114(3.11)	< 0.001
Others	17/129(13.18)	32/1114(2.87)	< 0.001
Brain MRI			
Abnormal throughout the course, n(%)	22/31(70.97)	168/246(68.29)	0.762
Cerebral hemisphere	12/31(38.71)	120/246(48.78)	0.290
Diecephalon	3/31(9.68)	26/246(10.57)	1.000
Cerebellum	4/31(12.90)	14/246(5.69)	0.251
Brainstem(area postrema)	13/31(41.94)	47/246(19.11)	0.004
Brainstem(periepiendymal)	5/31(16.13)	11/246(4.47)	0.027
Brainstem(others)	16/31(51.61)	82/246(33.33)	0.045
Optic nerve MRI			
Abnormal	5/7(71.43)	94/113(83.19)	0.778
> 1/2 optic nerve	2/7(28.57)	48/113(42.48)	0.742
Spinal MRI			
Abnormal throughout the course, n(%)	24/31(77.42)	292/345(84.67)	0.293

NMOSD: neuromyelitis optica spectrum disorders; NMOSD-NOSIS: NMOSD with non-opticospinal manifestations as initial symptoms; NMOSD-OSIS: NMOSD with opticospinal manifestations as initial symptoms; ON:optic neurotis; MY:myelitis; ARR:annual relapse rate; CSF:cerebral spinal fluid; EDSS:expanded disability status scale;MRI:magnetic resonance imaging; LETM:longitudinal extensive transverse myelitis.

	NMOSD-NOSIS n = 33	NMOSD-OSIS n = 381	P value
LETM	17/31(54.84)	253/345(73.33)	0.028
Cervical segments	14/31(45.16)	84/345(24.35)	0.011
Thoracic segments	1/31(3.23)	62/345(17.97)	0.035
Cervical + thoracic segments	9/31(29.03)	147/345(42.61)	0.142

NMOSD: neuromyelitis optica spectrum disorders; NMOSD-NOSIS: NMOSD with non-opticospinal manifestations as initial symptoms; NMOSD-OSIS: NMOSD with opticospinal manifestations as initial symptoms; ON:optic neurotis; MY:myelitis; ARR:annual relapse rate; CSF:cerebral spinal fluid; EDSS:expanded disability status scale;MRI:magnetic resonance imaging; LETM:longitudinal extensive transverse myelitis.

Brainstem lesions were more commonly present in NMOSD-NOSIS patients than in NMOSD-OSIS patients (Brainstem [area postrema]: 41.94% vs. 19.11%, P = 0.004; Brainstem [periependymal]: 16.13% vs. 4.47%, P = 0.027; Brainstem [others]: 51.61% vs. 33.33%, P = 0.045). NMOSD-NOSIS patients had less frequent longitudinally extensive transverse myelitis (LETM) and were more likely to have cervical spinal cord lesions, and they were less likely to have thoracic spinal cord lesions than NMOSD-OSIS patients (LETM: 54.84% vs. 73.33%, P = 0.028; cervical segment: 45.16% vs. 24.35%, P = 0.011; thoracic segment: 3.23% vs. 17.97%, P = 0.035) (Table 2).

Evaluation of pre- and post-treatment ARRs for the main treatment modalities between NMOSD-NOSIS and NMOSD-OSIS patients is shown in Table 3. Three-hundred-and-three patients treated with immunosuppressive agents for more than 1 year were included in the analysis; 178 were administered azathioprine (2 mg/kg daily), 105 were given mycophenolate mofetil (1 g/day), and 20 were given rituximab (500 mg through intravenous infusion, repeated 2 weeks later. This cycle was repeated every 6 months [4 cycles in total for each patient]). Both NMOSD-NOSIS and NMOSD-OSIS patients responded well to all three drugs without any significant differences between the two groups.

Table 3
Evaluation of pre- and post-treatment ARRs in NMOSD-NOSIS and NMOSD-OSIS (serumpositive for AQP4)

Treatment	Therapy duration,y	Patient groups(n)	Pre-treatment	Post-treatment	P value	Relapse-free within 1 year, n(%)	Relapse-free within 2 year, n(%)
Azathioprine	2.00(1.00,6.00)	NMOSD-NOSIS n = 17	2.00(0.20,5.00)	0.50(0,2.00)	0.003	11/17(64.71)	7/16(43.75)
	4.00(1.00,17.00)	NMOSD-OSIS n = 161	1.00(0,4.00)	0.27(0,3.00)	< 0.001	103/160(64.38)	70/138(50.72)
Mycophenolate mofetil	2.00(1.00,4.00)	NMOSD-NOSIS n = 10	2.00(0.44,3.00)	0.25(0,1.00)	0.008	8/10(80.00)	4/9(44.44)
	2.00(1.00,4.00)	NMOSD-OSIS n = 95	0.80(0.27,4.00)	0(0,2.00)	< 0.001	77/95(81.05)	38/75(50.67)
Rituximab	1.00(1.00,1.00)	NMOSD-NOSIS n = 3	1.25(0.67,2.00)	0(0,1.00)	0.285	2/3(66.67)	–
	2.00(1.00,3.00)	NMOSD-OSIS n = 17	1.00(0.53,4.00)	0.33(0.2.00)	0.055	10/17(58.82)	6/13(46.15)

NMOSD: neuromyelitis optica spectrum disorders; NMOSD-NOSIS: NMOSD with non-opticospinal manifestations as initial symptoms; NMOSD-OSIS: NMOSD with opticospinal manifestations as initial symptoms; ARR:annual relapse rate. P:comparison of pre- and post-treatment ARR.

4. Discussion

Since the clinical characteristics and long-term outcomes of patients with NMOSD-NOSIS remain unknown, we retrospectively evaluated such patients in comparison with NMOSD-OSIS patients. Whereas it was not clear whether all patients with NMOSD-NOSIS will eventually develop ON/MY, our research showed that the majority do (88.37%). Only 11.63% of the total patients with NMOSD-NOSIS had non-opticospinal manifestations throughout the disease course. However, the disease duration of NMOSD-NOSIS patients who showed restricted non-opticospinal manifestations was shorter than that of NMOSD-NOSIS patients who did not develop ON/MY until the most recent follow-up; thus, it is possible that these NMOSD-NOSIS patients with restricted non-opticospinal manifestations will develop ON/MY before subsequent follow-ups.

NMOSD—NOSIS is easily misdiagnosed as Wernicke encephalopathy (peri-third ventricle region involvement), GBS (medulla oblongata involvement), digestive system diseases (area postrema involvement), etc. As NMOSD-NOSIS patients have a high probability of developing ON/MY, it is important to recognize that NMOSD can initially present with non-opticospinal symptoms. Our study showed that all the non-opticospinal manifestations in NMOSD were brain/brainstem symptoms. Most of the non-opticospinal manifestations were area postrema syndrome (vomiting and hiccups), acute brainstem syndrome (vertigo, diplopia), and acute diencephalic syndrome (somnolence), which are now recognized as among the most common core clinical characteristics of NMOSD, in addition to ON and LETM, and have been included in the newly proposed diagnostic criteria.[5, 6] More importantly, we identified other non-opticospinal manifestations, such as ataxia, facial paralysis, facial hypoesthesia, headache, psychiatric symptoms, limb spasms, and tinnitus, and the causative lesions were located in the cerebellum, brachium pontis, thalamus, and other nonspecific parts of brainstem. These symptoms and their responsible lesions expand our understanding of the spectrum of initial symptoms of NMOSD, which may facilitate early recognition of NMOSD-NOSIS patients.

Both non-opticospinal symptoms and associated medullary MRI lesions, particularly in the peri-third/fourth ventricle areas (diencephalon and area postrema), were reversible in many NMOSD—NOSIS patients. Compared with opticospinal symptoms, non-opticospinal symptoms recovered better. The CR rate of non-opticospinal symptoms was higher than that of opticospinal symptoms. Most of the lesions near the third and fourth ventricles (area postrema and diencephalon) resolved during follow-up. In addition, 12 patients presented vomiting and hiccup as initial symptoms (suggesting area postrema involvement, but brain MRI was not performed at the time of onset). During the follow-up, no area postrema lesions were found on their brain MRI, suggesting that area postrema lesions may have disappeared.

It is worth noting that five NMOSD-NOSIS patients had a normal appearance on brain MRI when they complained of hiccups and vomiting. It is conceivable that the early timing of the brain imaging may have missed evolving lesions. This postulation is supported by the observation that medullary lesions were detected in subsequent MRI in one patient when she initially presented with an area postrema syndrome 6 months prior. Another possible explanation is that the lesions were too small to be detected by MRI. Therefore, if a patient complains of nausea, vomiting, or other brainstem symptoms, which cannot be explained clinically and with normal-appearing MR images, the possibility of NMOSD should always be considered, and serum AQP4 antibody should be assessed.

The clinical characteristics of NMOSD-NOSIS patients differed from those of NMOSD-OSIS patients. NMOSD-NOSIS patients had a younger onset age and lower serum AQP4 titers than NMOSD-OSIS patients. Although NMOSD-NOSIS patients may develop ON/MY during follow-up, the frequency of non-ON/MY relapse episodes remained higher than that in NMOSD-OSIS patients. NMOSD-NOSIS patients more commonly had brainstem lesions, more cervical and less thoracic involvement, and less frequent LETM, than NMOSD-OSIS patients.

NMOSD-NOSIS patients had better long-term clinical outcomes. NMOSD-NOSIS patients had lower EDSS scores at follow-up and took longer to reach EDSS 3.0 than NMOSD-OSIS patients, which may be due to the following reasons: 1) The brain lesions in NMOSD-NOSIS patients were mostly concentrated in the peri-third/fourth ventricle (diencephalon and area postrema) or periependymal areas in the brainstem, avoiding the pyramidal tract, and thus had little effect on motor function. 2) NMOSD-NOSIS patients had a younger age of onset than NMOSD-OSIS patients. Several previous studies have reported poor clinical outcomes in older-onset patients with NMOSD.[8, 9] 3) The immunopathogenesis for NMO lesions in the peri-third/fourth ventricle areas may be different from the typically destructive NMO lesions that predominate in the optic nerves or spinal cord. Immunohistochemical analyses of archival brain, spinal cord, and optic nerve tissues obtained from patients with NMO have demonstrated a novel NMO lesion phenotype in the medullary floor of the fourth ventricle (including the area postrema), which exhibits loss of AQP4 and

contains inflammatory cells, but lacks demyelination or necrosis.[10, 11] We further hypothesized that binding of NMO-IgG to AQP4 in the peri-third/fourth ventricle areas may be less efficient at activating complement. The peri-third/fourth ventricle areas in the brainstem are close to the cerebrospinal fluid circulation system, and these circumventricular neural structures are devoid of a blood–brain barrier (BBB)[12, 13]. This anatomical site could thus serve as a portal for circulating AQP4-IgG entry into the cerebrospinal fluid, reducing the concentration of AQP4-IgG in the local central nerve tissue in these areas, as well as the inflammatory response and neurological damage in these areas. The finding that NMO lesions near the third/fourth ventricles recovered better than those further away support our hypothesis. This hypothesis may also partly explain why serum anti-AQP4 titers in NMOSD-NOSIS patients were lower than those in NMOSD-OSIS patients in our study: the circulating AQP4 antibody entered the cerebrospinal fluid circulation through the weak BBB in the peri-third/fourth ventricle areas, thus reducing the serum AQP4 antibody titers in NMOSD-NOSIS patients.

The limitation of this study is that the sample size of NMOSD-NOSIS cases was relatively small; however, the long-term follow-up of these cases revealed the clinical characteristics and outcomes of NMOSD-NOSIS patients to a large extent.

5. Conclusion

Patients with NMOSD with NOSIS have younger age of onset, lower serum AQP4 antibody titers, and better clinical outcomes.

Declarations

Conflict of interest

The authors report no disclosures relevant to the manuscript.

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Figures

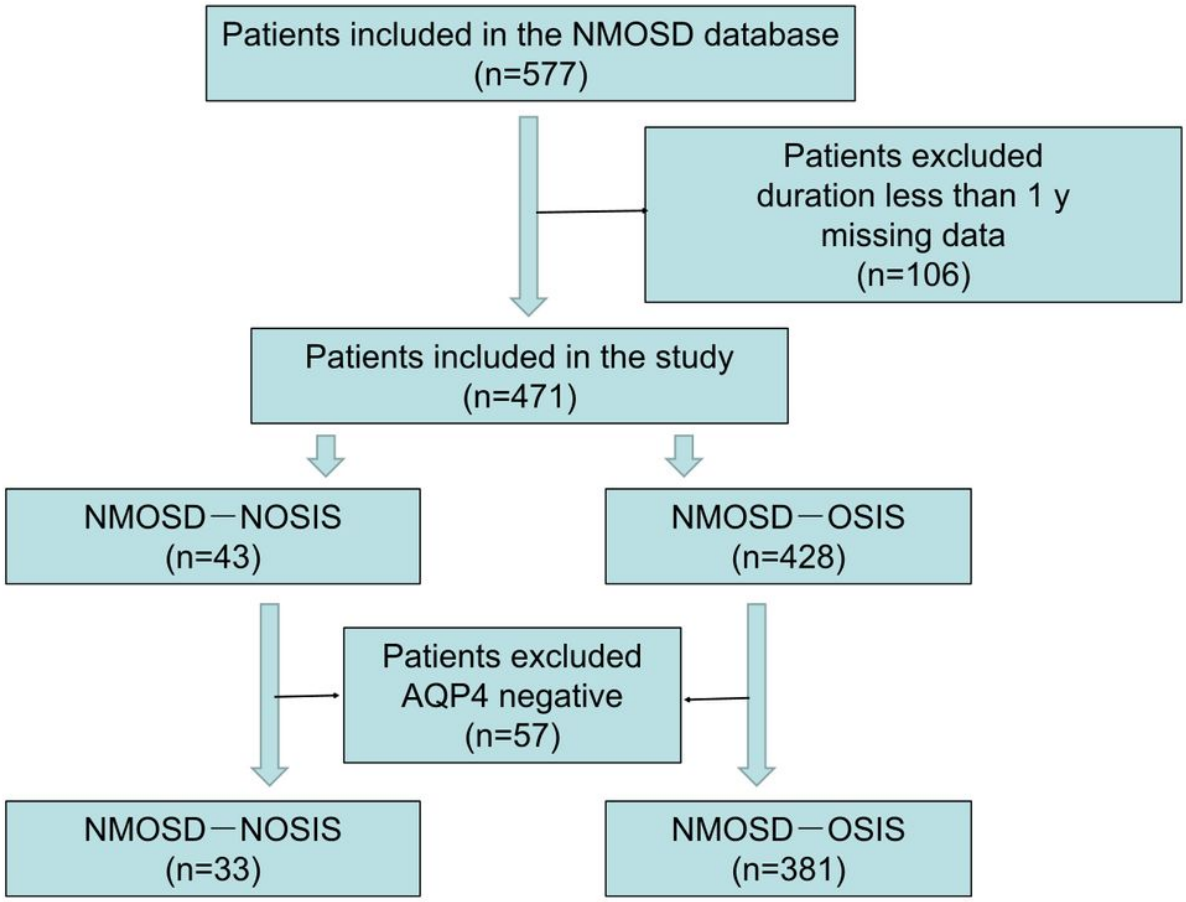

Figure 1

Study flow chart. NMOSD: neuromyelitis optica spectrum disorders; NMOSD-NOSIS: NMOSD with non-opticospinal manifestations as initial symptoms; NMOSD-OSIS: NMOSD with opticospinal manifestations as initial symptoms.

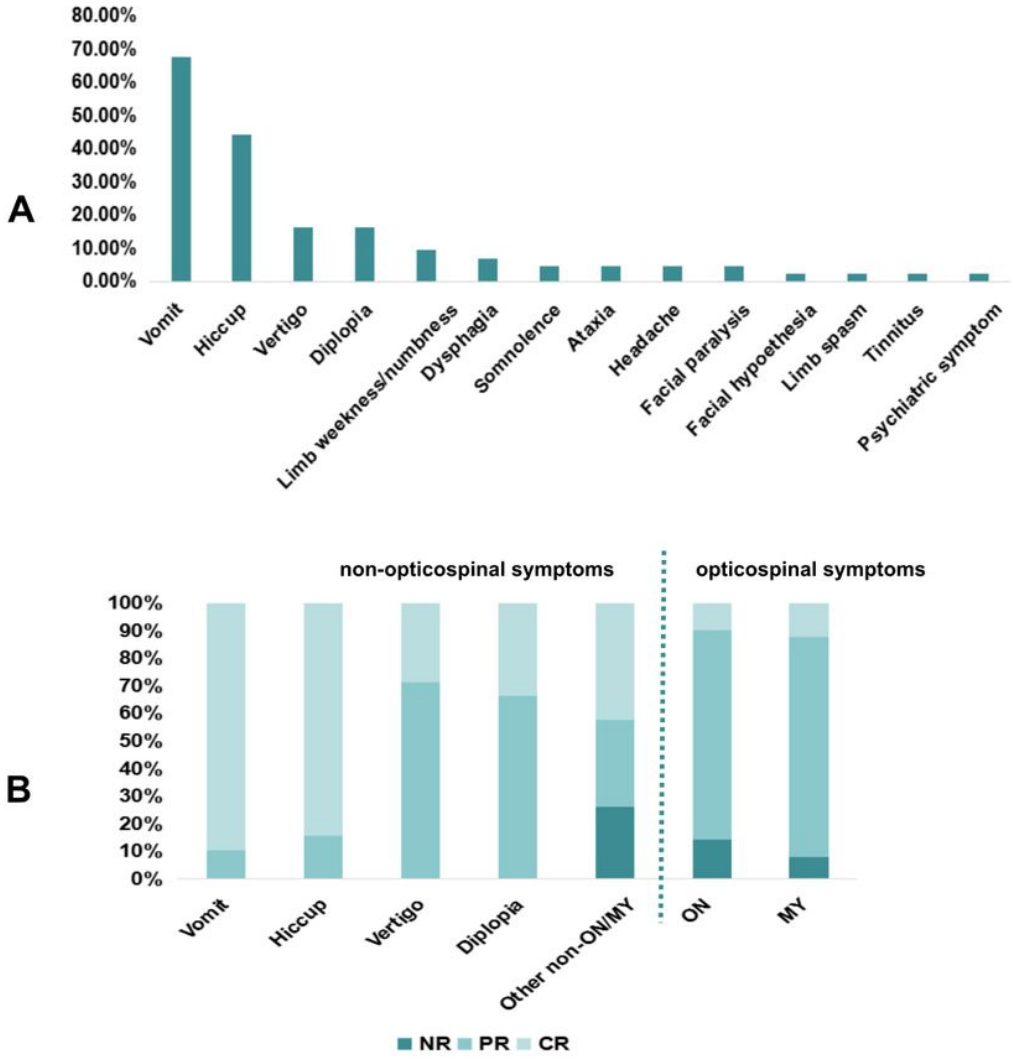

Figure 2

Analysis of non-opticospinal and opticospinal symptoms in NMOSD-NOSIS. A: The composition of non-opticospinal initial symptoms in NMOSD-NOSIS; B: The comparison of recovery between non-opticospinal initial symptoms and opticospinal symptoms in NMOSD-NOSIS. ON:optic neuritis; MY: myelitis; NR: no remission; PR: partial remission; CR: complete remission; NOSIS: non-opticospinal manifestation as initial symptoms; NMOSD-NOSIS: NMOSD with non-opticospinal manifestations as initial symptoms.

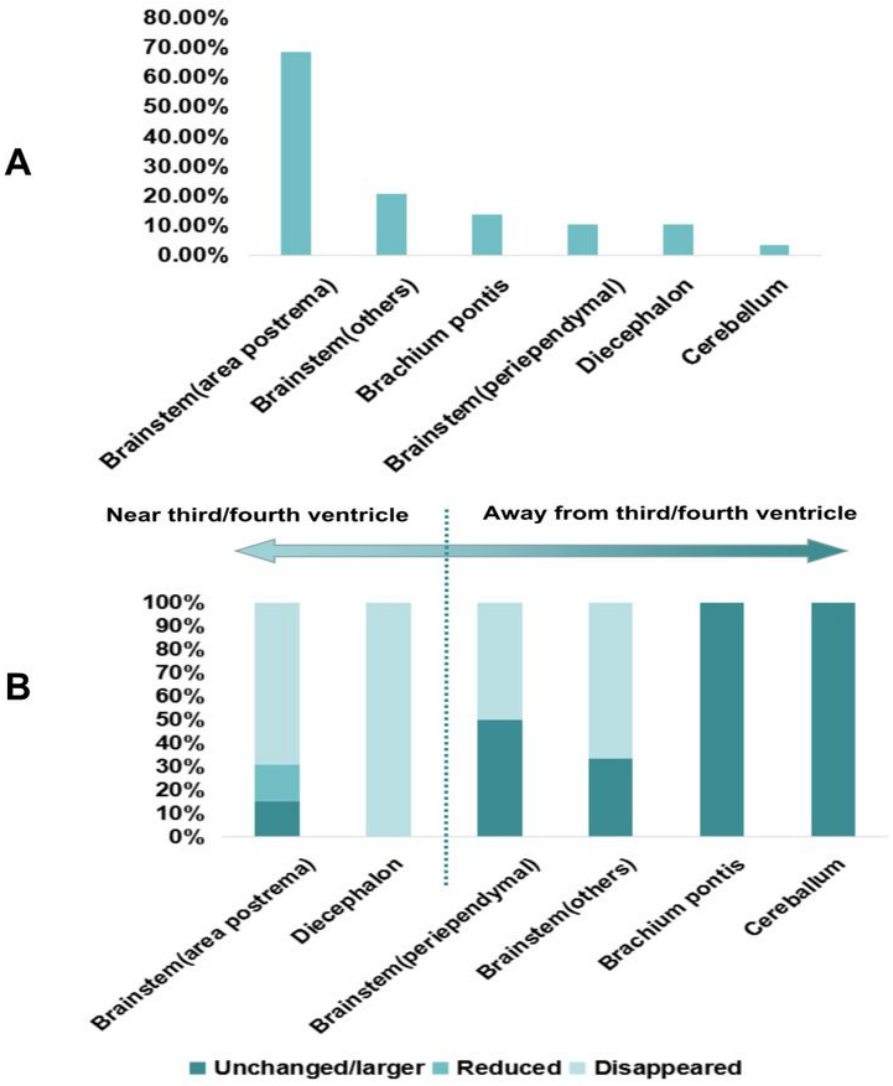

Figure 3

Responsible lesions for non-opticospinal initial symptoms in brain MRI and changes after follow-up in NMOSD-NOSIS. A: Responsible lesions for non-opticospinal initial symptoms detected in brain MRI in NMOSD-NOSIS; B: Changes of responsible lesions for non-opticospinal initial symptoms in NMOSD-NOSIS after follow-up. NMOSD-NOSIS: NMOSD with non-opticospinal manifestations as initial symptoms.

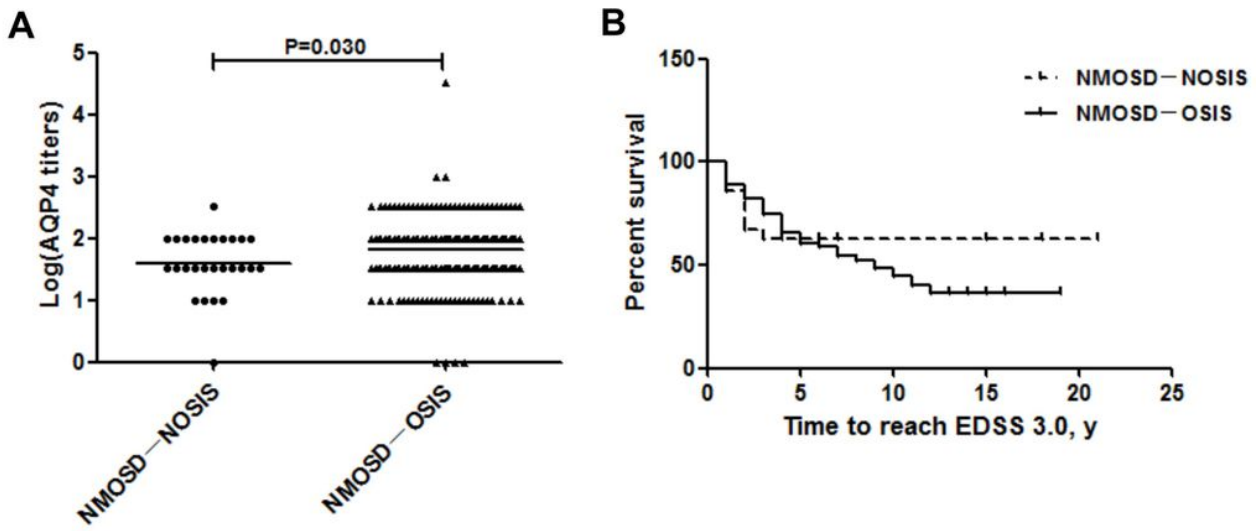

Figure 4

Comparison of serum AQP4 titers and time to reach EDSS 3.0 between NMOSD-NOSIS and NMOSD-OSIS. A: Comparison of serum AQP4 titers between NMOSD-NOSIS and NMOSD-OSIS; B: Comparison of time to reach EDSS 3.0 between NMOSD-NOSIS and NMOSD-OSIS. NMOSD-NOSIS: NMOSD with non-opticospinal manifestations as initial symptoms; NMOSD-OSIS: NMOSD with opticospinal manifestations as initial symptoms.