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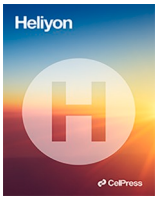

Research article

Neuromyelitis optica spectrum disorder with acute brainstem manifestations as initial symptoms

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ABSTRACT

Objective: To explore the clinical features and prognosis of patients with neuromyelitis optica spectrum disorder (NMOSD) initially presenting with acute brainstem symptoms.
Methods: The clinical data of NMOSD patients admitted to two medical centers were collected. The clinical characteristics, laboratory data, neuroimaging features and prognoses of patients with NMOSD with acute brainstem manifestations as initial symptoms (NMOSD-BSMIS) were analyzed. The clinical features and prognosis of patients with NMOSD-BSMIS and patients with NMOSD with other manifestations as initial symptoms (NMOSD-OMIS) were compared.
Results: Fifty-two patients (18.37 %, 52/283) initially presented with acute brainstem symptoms. Intractable nausea, vomiting or hiccups, diplopia, vertigo, headache, and facial hypoesthesia were the initial symptoms in most of the patients. The percentage of patients who were positive for serum aquaporin 4 (AQP4)-IgG antibodies was 81.63 % (40/49). MRI revealed that the lesions were usually located in the postrema, dorsal medulla oblongata, pons and other areas around the fourth ventricle. The early-stage misdiagnosis rate was 46.15 %. Compared with those in the non-misdiagnosed group, the age of onset of patients in the NMOSD-BSMIS group was older, and the proportion of patients admitted to the neurology department as the first department was lower in the misdiagnosed group. The annual relapse rate of patients who underwent NMOSD-BSMIS was significantly greater than that of patients who underwent NMOSD-OMIS ($P < 0.01$).
Conclusions: NMOSD patients can initially present with different brainstem symptoms. The early misdiagnosis rate of NMOSD-BSMIS is high. Moreover, if patients are older or initially admitted to nonneurological departments, they are more likely to be misdiagnosed. Moreover, the annual recurrence rate of NMOSD-BSMIS is greater in the early stage.

Neuromyelitis optica spectrum disorder (NMOSD) is an immune-mediated inflammatory demyelinating disease of the central nervous system. Aquaporin 4 (AQP4) immunoglobulin G antibodies are relatively specific humoral markers for such diseases [1]. In 2015, the International Panel for Neuromyelitis Optica Diagnosis (IPND) published revised diagnostic criteria for NMOSD, which

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includes 6 core clinical symptoms: optic neuritis, myelitis, area postrema syndrome, other acute brainstem syndromes, narcolepsy or acute diencephalic syndrome with lesions revealed on MRI, and cerebral syndrome with lesions revealed on MRI [2]. In AQP4 antibody-positive NMOSD patients, the incidence of optic neuritis or myelitis was greater than that of other symptoms, as shown in a large international cohort study [3]. Although brainstem lesions in NMOSD patients have been widely reported, there are few studies on NMOSD-BSMIS. In addition, patients with NMOSD who lack typical symptoms of optic neuritis and myelitis are easily misdiagnosed in the early stage [4–6], which is not conducive to the treatment and prognosis of patients. A total of 52 patients with NMOSD-BSMIS from two medical centers were included in the present study to explore the clinical features, rate of misdiagnosis and prognosis of NMOSD-BSMIS. Our study may provide insight into the pathogenesis and facilitate early recognition of NMOSD-BSMIS.

1. Methods

1.1. Patients

Patients with NMOSD who were admitted to the Affiliated Hospital of Xuzhou Medical University from January 1, 2015, to August 1, 2022, or the Affiliated Brain Hospital of Nanjing Medical University from January 1, 2016, to August 1, 2022, were included. Patients were followed up in our study by appointment for admission, outpatient visits and patient initiative to seek care. Follow-up was performed by two neurologists. The participants included were divided into those with NMOSD with acute brainstem manifestations as initial symptoms (NMOSD-BSMIS) and those with NMOSD with other manifestations as initial symptoms (NMOSD-OMIS). NMOSD-BSMIS patients were divided into a non-misdiagnosed group and a misdiagnosed group. According to the presence of AQP4-IgG, NMOSD-BSMIS patients were divided into groups with AQP4-IgG and groups without AQP4-IgG.

1.2. Inclusion and exclusion criteria

Patients who met the NMOSD diagnostic criteria published by the IPND in 2015 were included (patients previously diagnosed according to the 2006 Wingerchuk diagnostic criteria [7] were reconfirmed according to the 2015 criteria). Furthermore, the follow-up or last visit of all participants was more than 1 year after symptom onset. Patients with a history of other serious central nervous system diseases or insufficient information, such as a duration of disease <1 year, or a lack of neuroimaging data, were excluded. Two neurologists reviewed medical records and confirmed that the inclusion and exclusion criteria were met.

1.3. Data collection

The following clinical data of the participants were reviewed and collected retrospectively: sex, age of onset, initial symptoms, laboratory findings, MRI findings, first visit department, misdiagnosis condition, Expanded Disability Status Scale (EDSS) scores at the last follow-up or hospital discharge, presence of a spinal cord lesion $\geq$ three vertebrae (at most recent follow-up or hospital discharge), duration of follow-up (duration from symptom onset to last follow-up or hospital discharge), number of relapses, and annual relapse rate (ARR). A new neurological deficit that lasted more than 1 day and occurred more than 1 month after the previous episode was defined as a relapse [8]. Serum AQP4 IgG antibodies were measured with commercial sampling kits via cell-based assays. Among the participants, routine laboratory tests and immunological tests were performed. MRI scans of the brain and spinal cord were performed with multiple imaging parameters: T1W images with or without gadolinium, T2W images, diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences.

The data used in this study came from two different hospitals, but the same researchers reviewed medical records and collected data and confirmed that the inclusion and exclusion criteria were met. Serum AQP4 IgG antibody levels in participants from the two hospitals were measured by cell-based assays. MRI scans were both performed on 3.0 T or 1.5 T MRI scanners. Other routine blood and cerebrospinal fluid examination methods used in the two hospitals were similar.

1.4. Statistical analysis

SPSS 22.0 (Chicago, IL, USA) was used for statistical analysis. Continuous variables that conformed to a normal distribution are presented as the mean $\pm$ standard deviation. Continuous variables that did not conform to the normal distribution are presented as medians and interquartile ranges (IQRs). Categorical variables are described by absolute numbers (rates). Independent two-sample Student's t tests or Wilcoxon Mann–Whitney U tests were used to compare continuous data between two groups, and Chi-square tests and adjusted chi-square tests were used to compare categorical data. A P value < 0.05 indicated that the difference was statistically significant.

2. Results

2.1. Clinical characteristics, laboratory examinations and neuroimaging features of patients with NMOSD-BSMIS

A total of 283 patients were included in the study. Patients with NMOSD-BSMIS accounted for 18.37 % (52/283) of the patients. All participants were Han Chinese. Among the 52 patients, 41 patients were female (78.85 %), and 11 patients were male (21.15 %). The age of onset ranged from 12 to 87 (43.48 $\pm$ 17.03) years. The most common initial symptoms were vomiting and nausea (21/52),

followed by hiccup (12/52), diplopia (10/52), vertigo (8/52), headache (7/52), facial hypoesthesia (7/52), limb numbness (7/52), limb weakness (4/52), dysarthria (4/52), bucking (4/52), dysphagia (3/52), ataxia (3/52), facial pruritus (1/52), psychiatric symptoms (1/52), and consciousness disorder (1/52) (Fig. 1).

Blood examinations: Among the 49 patients (antibodies were not measured in 3 participants), 40 patients' serum AQP4-IgG antibodies were positive, and the serum AQP4-IgG positivity rate was 81.63 %. A total of 32 patients were tested for myelin oligodendrocyte glycoprotein (MOG) antibodies, and only 1 patient's serum was positive for MOG antibodies; this patient's serum AQP4-IgG antibodies were negative. For other serum autoimmune antibodies, 11 patients' serum anti-ANA antibodies were positive, 8 patients' serum anti-SSA antibodies were positive, 4 patients' anti-SSB antibodies were positive, 3 patients' serum anti-O antibodies were positive, and 3 patients' serum rheumatoid factor (RF) levels were positive. In addition, the serum of 6 patients was positive for antithyroglobulin (TGAb), that of 4 patients was positive for thyroid peroxidase antibodies (TPOAb), and that of 1 patient was positive for thyrotrophin receptor antibodies (TRAb). The proportion of patients with other positive serum antibodies was 38.46 %. There were five patients with coexisting autoimmune diseases: three with Sjogren's syndrome, one with systemic lupus erythematosus (SLE), and one with Hashimoto's thyroiditis. The proportion of patients with coexisting autoimmune diseases was 9.62 %.

Cerebrospinal fluid examinations: Leukocytes were normal or mildly increased (64.70 % vs. 35.29 %), leukocytes were greater than 50×10^6/L in 2 patients, and lymphocytes increased significantly. In addition, total protein was normal or slightly increased (61.76 % vs. 38.24 %). The proportion of patients with increased IgA in cerebrospinal fluid was 20.59 %, that with increased IgM was 23.53 %, and that with increased IgG was 52.94 %. Cerebrospinal fluid oligoclonal band examination of 27 patients showed that oligoclonal bands were all negative.

Neuroimaging features: Brain magnetic resonance imaging (MRI) revealed that the lesions were mostly located in the postrema, dorsal medulla oblongata, pons and other areas around the fourth ventricle (Fig. 2). The brainstem lesions were mostly high-signal on T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), fluid-attenuated inversion recovery (FLAIR), and iso-signal or slightly high-signal on diffusion-weighted imaging (DWI). Gadolinium enhancement was observed in a few patients. In 16 (30.77 %) patients with NMOSD-BSMIS, a contiguous brainstem lesion extending into the cervical spinal cord was observed. There were typical imaging findings (Fig. 3 An ~ D). Two cases involved lesions along the brain and brain stem (Fig. 4 An ~ D). There were complete images with follow-up images of two patients (Fig. 5 An ~ D).

Young woman with chief complaints of alalia, vomiting, hearing loss for 3 days, AQP4-IgG antibodies+, lesions in bilateral thalamus, hypothalamus (**A**) and anterior wall of the fourth ventricle (**B**). Young woman with chief complaints of right limb weakness, alalia for 2 days, AQP4-IgG antibodies+, lesions in the left mesencephalon (**C**) and bilateral centrum semiovale (**D**).

A young woman with a chief complaint of diplopia for 1 day and an AQP4-IgG antibody + lesion in the left pons (**A**). After glucocorticoid treatment, she improved, and her symptoms disappeared. Two years later, the patient presented with numbness in both lower limbs and dysuria, and the lesion was in the thoracic cord (**B**). A young woman with a chief complaint of recurrent vomiting for 1 week and an AQP4-IgG antibody + lesion in the medulla oblongata (**C**). After glucocorticoid treatment, she improved, and her symptoms disappeared. At follow-up after 1.5 years, the patient had no new symptoms, and the old lesions were in the medulla oblongata (**D**).

The first visit to the department and misdiagnosis

Among the first visit departments of the 52 patients with NMOSD-BSMIS, 40 were neurology departments, 9 were gastroenterology departments, 1 was neurosurgery, 1 was otolaryngology, and 1 was rheumatology and immunology. Early-stage misdiagnosis occurred in 24 patients, accounting for 46.15 % of the patients.

To compare the clinical characteristics and prognoses of 52 patients with NMOSD-BSMIS in the misdiagnosed group and the non-misdiagnosed group.

There was no significant difference between the two groups in terms of sex, the proportion of vomiting/hiccups as initial symptoms, the percentage of patients positive for AQP4-IgG antibodies, the proportion of patients positive for other serum autoimmune

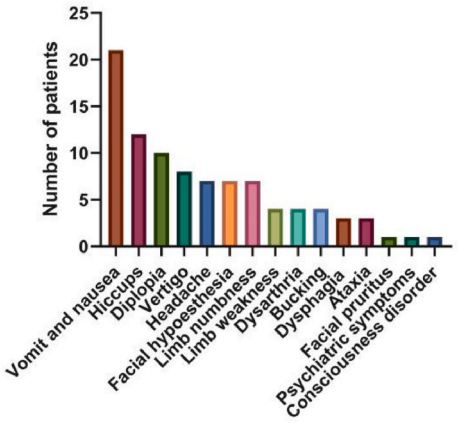

Fig. 1. The composition of initial symptoms in 52 patients with NMOSD who initially presented with acute brainstem symptoms.

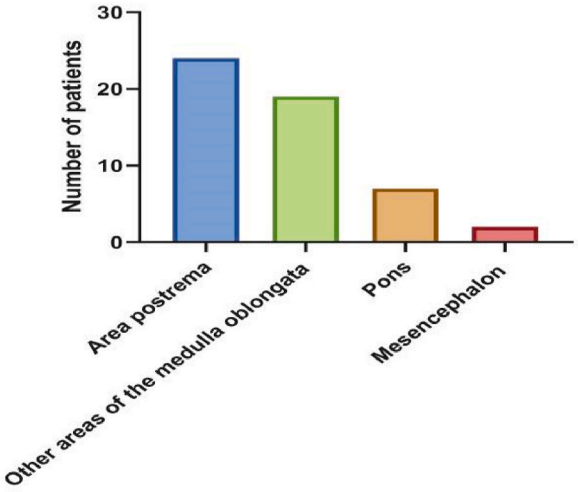

Fig. 2. Responsible lesions for initial brainstem symptoms revealed on MRI of the 52 patients.

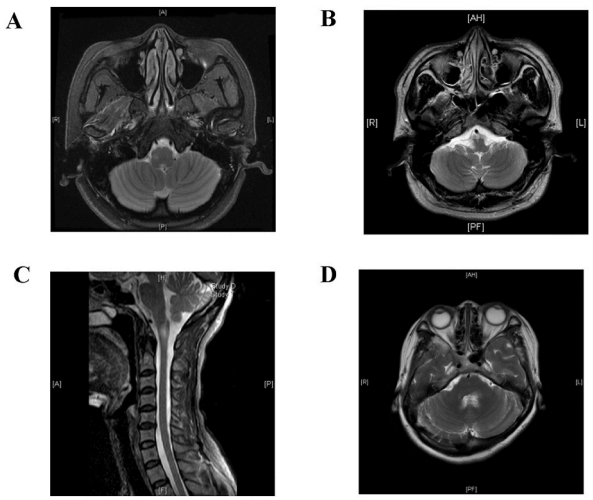

Fig. 3. (A–D) Lesions in NMOSD-BSMIS on T2W. A Lesions in the postrema area. **B** Lesions in the dorsal medulla oblongata. **C** Medulla oblongata lesions extending into the cervical spinal cord. **D** Lesions in the pons tegmentum adjacent to the fourth ventricle.

antibodies, the proportion of brainstem lesions extending to the cervical spinal cord, or the annual relapse rate (all $p > 0.05$). However, compared with that in the non-misdiagnosed group, the age of onset was greater ($p = 0.046$, <0.05), and the proportion of patients who visited the neurology department first was lower in the misdiagnosed group ($p < 0.001$). (Table 1).

To compare the clinical characteristics and prognosis of 49 patients with NMOSD-BSMIS between the AQP4-IgG group and the non-AQP4-IgG group.

Because the presence of AQP4-IgG antibodies was unknown in 3 participants, data from 49 participants were analyzed. There was no significant difference between the two groups in terms of sex, age of onset, the proportion of patients with vomiting/hiccups as initial symptoms, the presence of other serum autoimmune antibodies, the presence of brainstem lesions extending to the cervical spinal cord, the presence of spinal cord lesions ≥ three vertebrae, an EDSS score ≥5 or the annual relapse rate (all $p > 0.05$). (Table 2).

Relapse and prognosis

The 52 patients were followed up for 3.5 (2.5, 5) years. The annual relapse rate of patients who underwent NMOSD-BSMIS was 0.5 (0.125, 0.75) times/year. Among the 52 patients, 5 patients relapsed due to the discontinuation of hormones and immunosuppressants, 5 patients had a history of upper respiratory tract infection before relapse, 2 patients had a history of overwork before relapse, and the remaining 41 patients had no obvious precipitating factor. At the last follow-up visit or hospital discharge, 23 (44.23 %) patients had spinal cord lesions in ≥ three vertebrae on MRI. According to the Extended Disability Status Scale (EDSS) scores at the last follow-up visit or hospital discharge, patients were divided into low scores group (<5.0 points) and high scores group (≥5.0 points). There were 18 patients in the high-score group, accounting for 34.62 %.

To compare the clinical features and prognoses of the NMOSD-BSMIS group and NMOSD-OMIS group.

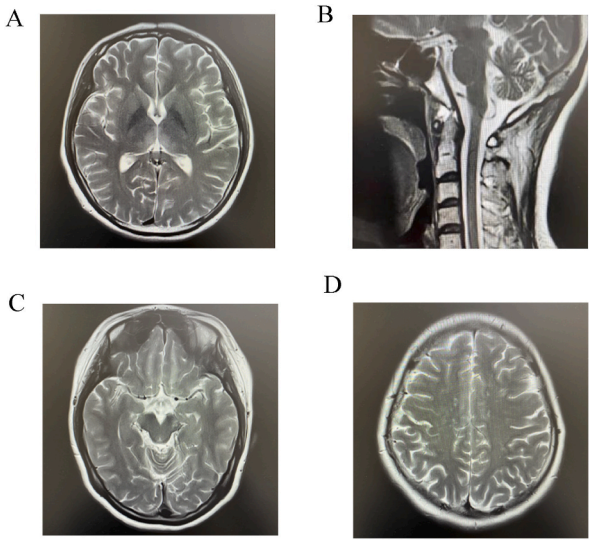

Fig. 4. (A–D) Lesions along the brain and brainstem of two patients with NMOSD-BSMIS on T2W.

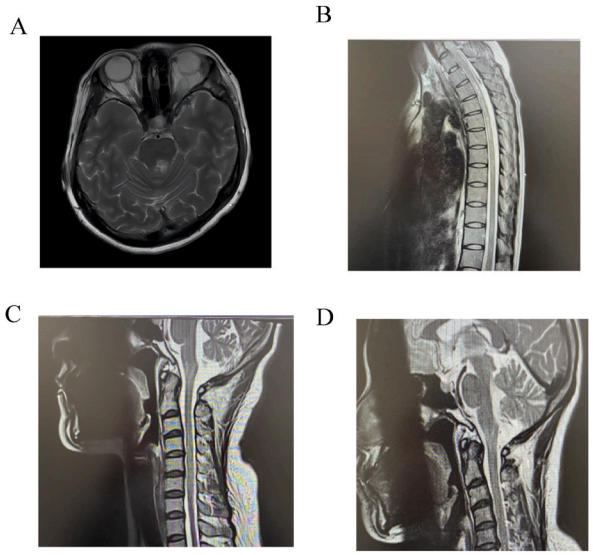

Fig. 5. (A–D) Magnetic resonance T2 images with follow-up images of two patients with NMOSD-BSMIS.

There were 283 patients with NMOSD included in our study, none of whom initially presented with narcolepsy, acute diencephalic syndrome or cerebral syndrome. All 231 patients with NMOSD-OMIS initially presented with opticospinal syndrome. There was no significant difference between the two groups in terms of sex, age of onset, percentage of patients with positive AQP4-IgG antibodies, duration of follow-up, proportion of patients with spinal cord lesions $\geq$ three vertebrae or an EDSS score $\geq$5.0 at the last follow-up visit or hospital discharge (all $p > 0.05$). However, the annual relapse rate of the NMOSD-BSMIS group was significantly greater than that of the NMOSD-OMIS group ($p = 0.014$, <0.05). (Table 3).

3. Discussion

Patients with NMOSD usually present with optic neuritis and myelitis. However, recent studies have shown that the lesions of AQP4 antibody-positive patients with NMOSD can also be involved in the brainstem, diencephalon, and cerebrum [9,10]. A large international research showed that compared with Caucasians, Asians had a younger age of onset of NMOSD, and lesions were more likely to involve in intracranial structures, such as the brain/brainstem [11]. A high relapse rate and high mutation rate are important characteristics of NMOSD, an immune-inflammatory disease of the CNS. Therefore, early-stage identification, early-stage diagnosis, and standardized treatment are highly desirable. However, patients with NMOSD-BSMIS are more likely to be misdiagnosed. Therefore, we

Table 1
Comparison of the clinical characteristics and prognoses of 52 patients with NMOSD-BSMIS between the misdiagnosed group and the non-misdiagnosed group.

	misdiagnosed group (n = 24)	non-misdiagnosed group (n = 28)	*p*
female [*n* (%)]	21 (87.5)	20 (71.43)	0.283[b]
age of onset (year)	48.54 ± 15.94	39.14 ± 17.00	**0.046**[c]
neurology department as the first visit department [*n* (%)]	12 (50)	28 (100)	**< 0.001**[b]
vomiting/hiccup as initial symptoms [*n* (%)]	13 (54.17)	13 (46.43)	0.578[b]
AQP4-IgG + [*n* (%)]	19 (19/23) (82.61)	21 (21/26) (80.77)	1[b]
with other serum autoimmune antibodies	4 (16.67)	10 (35.71)	0.219[d]
brainstem lesions extending to the cervical spinal cord [*n* (%)][a]	7 (29.17)	9 (32.14)	0.817[b]
annual relapse rate (time/year)	0.55 (0.25, 0.94)	0.44 (0, 0.63)	0.262[e]

[a] MRI findings at the first visit.
[b] Chi-square test.
[c] Student's *t*-test.
[d] Adjusted chi-square test.
[e] Wilcoxon Mann–Whitney *U* test.

Table 2
Comparison of the clinical characteristics and prognoses of 49 patients with NMOSD-BSMIS between the group with AQP4-IgG and the group without AQP4-IgG.

	group with AQP4-IgG (n = 40)	group without AQP4-IgG (n = 9)	*p*
female [*n* (%)]	33 (82.5)	6 (66.67)	0.544[d]
age of onset (year)	44.78 ± 18.31	37.89 ± 11.82	0.288[e]
vomiting/hiccup as initial symptoms [*n* (%)]	20 (50.00)	5 (55.56)	1[d]
with other serum autoimmune antibodies	16 (40.00)	3 (33.33)	1[f]
brainstem lesions extending to the cervical spinal cord [*n* (%)][a]	14 (35.00)	2 (22.22)	0.730[f]
spinal cord lesions ≥ three vertebrae [n (%)][b]	18 (45.00)	5 (55.56)	0.839[d]
EDSS scores ≥5 [n (%)][c]	16 (40.00)	2 (22.22)	0.537[f]
annual relapse rate (time/year)	0.5 (0, 0.67)	0.5 ± 0.41	0.950[g]

[a] MRI findings at the first visit.
[b] Spinal cord lesions ≥ three vertebrae at the last follow-up or hospital discharge.
[c] Expanded Disability Status Scale (EDSS) scores at the last follow-up or hospital discharge.
[d] Chi-square test.
[e] Student's t-test.
[f] Adjusted chi-square test.
[g] Wilcoxon Mann–Whitney U test.

Table 3
Comparison of the clinical features and prognoses of the NMOSD-BSMIS group and the NMOSD-OMIS group.

	NMOSD-BSMIS(n = 52)	NMOSD-OMIS(n = 231)	*p*
female [*n* (%)]	41 (78.85)	195 (84.41)	0.330[d]
age of onset (year)	43.48 ± 17.03	33 (46, 56)	0.462[e]
AQP4-IgG + [*n* (%)]	40 (40/49) (81.63)	164 (164/225) (72.89)[a]	0.203[d]
duration of follow -up (year)	3.5 (2.5,5)	4 (3, 6)	0.253[e]
spinal cord lesions ≥ three vertebrae [n (%)][b]	23 (44.23)	124 (53.68)	0.258[d]
EDSS scores ≥5 [n (%)][c]	18 (34.62)	64 (27.70)	0.321[d]
annual relapse rate (time/year)	0.5 (0.125, 0.75)	0.286 (0, 0.5)	0.014[e]

[a] Antibodies were not measured in 6 participants.
[b] Spinal cord lesions ≥ three vertebrae at the last follow-up or hospital discharge.
[c] Expanded Disability Status Scale (EDSS) scores at the last follow-up or hospital discharge.
[d] Chi-square test.
[e] Wilcoxon Mann–Whitney U test.

reviewed and analyzed the characteristics of NMOSD-BSMIS patients.

The first manifestations of NMOSD in patients with symptoms of the brainstem, diencephalon, cerebrum and other intracranial lesions have been described in recent reports. A study from Australia and New Zealand reported by Bukhari W et al. showed that NMOSD patients with intracranial symptoms as the initial manifestation accounted for approximately 17 % of the total NMOSD patients [12]. In another study involving a total of 500 people in Japan, the proportion of NMOSD-BSMIS patients was 9.2 %, and the proportion of NMOSD patients with cerebrum lesion manifestations as initial symptoms was slightly lower (8.6 %) [13]. We found that the proportion of NMOSD-BSMIS confirmed by MR was 18.37 %, which was generally consistent with previous studies. The differences

may be related to the widespread use of AQP4-IgG antibody detection and MR technology and racial differences.

Among 52 NMOSD-BSMIS patients, 26 patients initially presented with intractable nausea, vomiting and/or hiccups, accounting for 50 %, which is considered to be an area postrema syndrome. At present, scholars believe that the area postrema the floor of the fourth ventricle is adjacent to the solitary tract nucleus, and there is information transmission between them, resulting in the area postrema involved in the regulation of the vomiting reflex [14]. The postrema area is filled with capillaries that lack tight endothelial junctions. Due to its weak blood–brain barrier and abundant expression of AQP4, AQP4 antibodies in the peripheral circulation are more likely to invade the brain, resulting in immune-inflammatory injury. AQP4 is also predominantly expressed in the area around the midbrain aqueduct and the fourth ventricle [15]. Therefore, due to differences in brainstem lesions caused by AQP4 antibodies, patients may also present with diplopia, vertigo, headache, and facial hypoesthesia as initial symptoms. Diplopia may be the second most common symptom of brainstem following area postrema syndrome [16–19], possibly because the nerve nuclei and fibers controlling eye movements are partly located in the dorsal brainstem around the ventricle where AQP4 is enriched. These symptoms are not specific, and early stage patients are easily misdiagnosed with other brainstem diseases, such as brainstem infarction and multiple sclerosis [20,21].

In our study, 81.63 % of the patients were AQP4 antibody-positive, suggesting that early-stage detection of serum AQP4 antibodies is helpful for identifying NMOSD-BSMIS patients. Previous reports have shown that many patients with NMOSD have coexisting autoimmune diseases, such as Sjögren's syndrome, systemic lupus erythematosus and rheumatoid arthritis [22,23]. This finding was similar to the findings in patients with NMOSD-BSMIS in our study. Autoimmune antibodies, such as anti-ANA antibodies, anti-SSA antibodies, rheumatoid factor, and TPOAb, were also detected in some patients, although there was no difference between the NMOSD-BSMIS and NMOSD-OMIS patients, which suggested that the immune system of NMOSD-BSMIS patients is unbalanced and disordered. Although MOG antibody-related diseases are increasingly recognized as independent and specific diseases, a recent meta-analysis revealed that in NMOSD patients with serum-negative AQP4-IgG, the percentage of MOG-Ab-positive patients was still high [24], suggesting that screening for MOG-Ab in AQP4-Ab-seronegative NMOSD patients is helpful for diagnosis and treatment. The mild changes in leukocytes in cerebrospinal fluid, total protein, and antibodies such as IgA, IgM, and IgG and negative results of the oligoclonal band test all suggested that cerebrospinal fluid examinations are helpful for the diagnosis and differential diagnosis of NMOSD-BSMIS.

MRI can clearly reveal the lesions of NMOSD-BSMIS patients. One explanation for the early-stage involvement of the brainstem is that immune inflammation itself begins in specific regions, such as the infratentorial region. In the early stages of the disease course, the immune tolerance of the relevant AQP4 is disrupted, resulting in the production of AQP4 antibodies in the peripheral blood. Thereafter, the blood–brain barrier is disrupted by nonspecific immune inflammation. At this time, the lesion location and disease phenotype of NMOSD are determined by the type of T lymphocytes infecting the central nervous system and the presence of AQP4 antibodies [16]. It was previously thought that long-segment cervical cord lesions extending into or with dorsal medulla lesions were specific signs of NMOSD. However, a recent study from the Mayo Clinic revealed that other long-segment extensive spinal cord lesions, such as sarcoidosis, can also extend into the dorsal medulla, and there was no statistically significant difference between them [25].

Compared with that in the non-misdiagnosed group, the age of onset was older in the misdiagnosed group. NMOSD is more common in young patients. Clinicians are more likely to consider neuroimmune diseases when admitting young patients with neurological deficit symptoms, so such patients are more likely to receive AQP4-IgG antibody detection and MRI examination early. Middle-aged and elderly patients were more likely to have gastrointestinal and cerebrovascular diseases. Long-term gastrointestinal symptoms, such as vomiting and hiccups, and symptoms of cerebral ischemia, such as dizziness and weakness, may affect the clinician's judgment. The proportion of patients who visited the neurology department first was lower in the misdiagnosis group. These findings suggest that patients are more likely to be misdiagnosed when they are admitted to nonneurological departments, such as gastroenterology and otolaryngology. The reason may be the insufficient understanding and underrecognition of such diseases for medical workers in other departments. Second, this difference may be related to the relatively mild or single symptoms of patients who were initially admitted to the nonneurological department. Recent studies have shown that the misdiagnosis of NMOSD is associated with a longer time needed to see a neuroimmunologist, a longer time needed to receive a first MRI scan and a negative aquaporin 4-IgG result. However, there was no significant difference between the two groups in terms of the percentage of AQP4-IgG-positive patients in our study, which may be related to the different subjects in the two studies (NMOSD-BSMIS, not NMOSD). Other influencing factors will be further explored in our future studies. In addition, there was no significant difference between the group with AQP4-IgG and the group without AQP4-IgG, which suggested that AQP4-iGg antibodies may not be associated with the prognosis of patients with NMOSD-BSMIS. However, the conclusions need to be further confirmed by large-sample and longitudinal studies.

In this study, there was no significant difference in the EDSS scores at the last follow-up visit or hospital discharge between the NMOSD-BSMIS and NMOSD-OMIS groups, which was consistent with the results of previous studies [5,6]. However, some studies have also shown that NMOSD patients with brainstem lesions seem to have higher EDSS scores, which predict more severe disability [10]. This difference may be related to the follow-up duration, disease duration, and sample size. With the progression of the disease, most NMOSD-BSMIS patients have lesions involving the optic nerve and spinal cord [5], which inevitably affects the EDSS score. We found that NMOSD-BSMIS patients had a greater annual relapse rate than NMOSD-OMIS patients, which may be related to the age of onset and AQP-4 antibody titers. Although some studies have suggested that AQP4-positive patients have a greater relapse rate and EDSS score [26,27], we did not find an obvious difference in the percentage of AQP4-positive patients between the two groups. Of course, our study did not consider the effect of differences in AQP4 antibody titers, and related research needs to be further advanced.

Although brainstem lesions in NMOSD patients have been widely reported, few studies have focused on the clinical characteristics and misdiagnosis rate of patients with NMOSD with acute brainstem manifestations as initial symptoms. In addition, our study was a two-center clinical study, and the data were obtained from two large medical centers in China. However, our study has the following

limitations. First, although our study was a bicenter clinical study, the overall sample size was small. Second, regarding diagnostic tests, our study did not consider exact AQP4 antibody titers. Third, the follow-up period in our study was short, and the prognostic assessment scale was relatively simple.

In conclusion, NMOSD-BSMIS patients usually present with intractable nausea, vomiting or hiccup, diplopia, vertigo, headache, facial hypoesthesia, limb weakness, limb numbness, dysarthria, etc., as initial symptoms. Lesions are usually located in the postrema, dorsal medulla oblongata, pons and other areas around the fourth ventricle. Misdiagnosis of NMOSD-BSMIS is common at the early stage of the disease, and it is more likely to occur when patients are older and initially admitted to a nonneurological department. Early-stage detection of serum AQP4 antibodies, cerebrospinal fluid examinations, and brain magnetic resonance imaging (MRI) are highly valuable for the diagnosis of such patients. Patients with NMOSD-BSMIS are more likely to experience relapse than patients with NMOSD-OMIS in the early stage.

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Ethics statement

The Medical Ethics Committee of the Affiliated Hospital of Xuzhou Medical University approved this study (APPROVAL NUMBER: XYFY2021-KL280-01; DATE: 2021-11-25).

Participant informed consent waivers for the study were approved by The Medical Ethics Committee of the Affiliated Hospital of Xuzhou Medical University. Because this study was an observational retrospective study, the previous clinical characteristics and follow-up data of the participants are collected for the study, and the written informed consent of the participants cannot be obtained. However, verbal informed consent for the publication of clinical features, laboratory tests, imaging examination, and follow-up data has been obtained from all participants by telephone, email, and other means. In addition, we declare that in addition to obtaining consent from parents/legal guardians, we have also obtained assent from all minors regarding the publication of the aforementioned clinical data.

Data availability statement

The data associated with our study were not deposited into a publicly available repository. However, the data that support the findings of this study are available upon reasonable request from the corresponding author, [Y P].

CRediT authorship contribution statement

Zhen Li: Writing – original draft, Conceptualization. **Minggang Yang:** Data curation. **Yang Pan:** Resources, Investigation, Funding acquisition. **Qi Fang:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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