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ORIGINAL PAPER

Comparison of Ocular Motor Findings Between Neuromyelitis Optica Spectrum Disorder and Multiple Sclerosis Involving the Brainstem and Cerebellum

Sun-Uk Lee[1,2] · Hyo-Jung Kim[3] · Jae-Hwan Choi[4] · Jeong-Yoon Choi[2,5] · Ji-Soo Kim[2,5]

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Abstract
This study aimed to define the clinical features and involved structures that aid in differentiation of neuromyelitis optica spectrum disorder (NMOSD) from multiple sclerosis (MS) involving the brainstem and cerebellum. We analyzed the clinical and ocular motor findings, and lesion distribution on brain MRIs in 42 patients with MS (17 men, mean age ± SD = 37 ± 12) and 26 with NMOSD (3 men, mean age ± SD = 43 ± 15) that were recruited from two university hospitals in South Korea (whole study population). An additional subgroup analysis was also conducted in 41 patients presenting acute brainstem or vestibular syndrome (brainstem syndrome population). Logistic regression analysis showed that bilaterality of the lesions ($p = 0.012$) and presence of horizontal gaze-evoked nystagmus (hGEN, $p = 0.041$) were more frequently associated with NMOSD than with MS in the whole study population. In the brainstem syndrome population, only hGEN ($p = 0.017$) was more frequent in NMOSD than in MS. The lesions specific for NMOSD were overlapped in the medial vestibular nucleus (MVN) and nucleus prepositus hypoglossi (NPH) at the pontomedullary junction. In conclusion, presence of hGEN and bilateral lesions involving the MVN and NPH favor the diagnosis of NMOSD rather than MS.

Keywords Vertigo · Nystagmus · Neuromyelitis optica spectrum disorder · Multiple sclerosis

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing demyelinating disorder characterized by optic neuritis, myelitis, and brain lesions [1]. Differentiation of NMOSD from multiple sclerosis (MS) is important to choose proper treatments and to minimize irreversible neural damage [2].

Even though introduction of serum anti-AQP4 antibody allowed a serological diagnosis of NMOSD in distinction from MS [3], 10–50% of patients with NMOSD are negative for anti-AQP4 antibody even with the most sensitive assay methods currently available [4]. Furthermore, more than a couple of weeks are required for the reports on serum anti-AQP4 antibody in most institutions. Therefore, other clinical, laboratorial, and radiologic findings are important for differentiation of NMOSD from MS especially during the acute phase.

The affected neural structures differ between NMOSD and MS. Indeed, MS is more likely to involve the structures adjacent to the lateral ventricle, the inferior temporal lobe, and the S-shaped/curved U-fibers [5]. In contrast, NMOSD tends to involve the neural structures around the 3rd and 4th ventricles that have an abundant expression of AQP4 [6]. This different lesion distribution would result in dissimilar clinical features between MS and NMOSD. Previously, the authors showed that lesions involving the dorsal medulla can present distinct ocular motor signs [7–10]. Given the proximity of the vestibular nuclear complex and area postrema that are

✉ Ji-Soo Kim
jisookim@snu.ac.kr

1 Department of Neurology, Korea University Anam Hospital, Seoul, South Korea

2 Department of Neurology, Seoul National University College of Medicine, Seoul, South Korea

3 Research Administration Team, Seoul National University Bundang Hospital, Seongnam, South Korea

4 Department of Neurology, Pusan National University School of Medicine, Pusan National University Yangsan Hospital, Yangsan, South Korea

5 Dizziness Center, Clinical Neuroscience Center, and Department of Neurology, Seoul National University Bundang Hospital, 173-82, Gumi-ro, Budang-gu, Seongnam, Gyeonggi-do 13620, South Korea

characteristically involved in NMOSD, we postulated that ocular motor findings may differ between NMOSD and MS indeed, 25% of NMOSD patients with intractable nausea/vomiting and hiccup accompany nystagmus [11]. In this study, we aimed to define the clinical features, especially the ocular motor findings and affected structures, for differentiation of NMOSD from MS involving the brainstem and cerebellum.

Subjects and Methods

Subjects

We reviewed the medical records of 250 patients with central inflammatory demyelinating diseases at two University Hospitals in Korea, Seoul National University Bundang Hospital from Apr 2003 to Mar 2018, and Pusan National University Yangsan Hospital from May 2011 to Mar 2018. Among them, 158 patients had the diagnosis of MS ($n = 94$) or NMOSD ($n = 64$, Fig. 1). The diagnosis of MS was made using the 2011 McDonald criteria [12]. NMOSD was diagnosed with the International Consensus Criteria [1]. Among the 158 patients, the brainstem or cerebellum was involved at least once in 78 patients (78/158 (49%); 51 in MS (51/94, 54%) and 27 in NMOSD (27/64, 42%)). After excluding 10 patients who had an initial evaluation of more than 2 weeks after symptom onset, 68 patients (42 with MS and 26 with NMOSD, 20 men, age range = 14–70 years, mean age ± SD = 39 ± 13) were finally included for analyses. In 16 patients who had experienced more than one attack from lesions involving the infratentorial structures (33 attacks), only the first attack was included for analyses.

We analyzed the clinical features in all 68 patients (whole study population), and also conducted a subgroup analysis for those initially presenting acute brainstem [13] or vestibular syndrome (brainstem syndrome population, $n = 41$). In addition to standard neurologic examination, patients also had ocular motor evaluation for spontaneous (SN), gaze-evoked (GEN), head-shaking (HSN), and positional nystagmus, saccades, smooth pursuit, and head-impulse tests (HITs) including video-oculography in 45 of the patients [14, 15]. The sera of the patients were tested for anti-AQP4 antibodies (1) at the Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, England, using cell-based assays ($n = 23$) [16], (2) with a kit (Euroimmun AG, Lubeck, Germany) according to the manufacturer's instructions ($n = 16$), or (3) using an indirect immunofluorescence assay ($n = 3$) [3].

Patients also had bithermal caloric tests, measurements of ocular torsion and subjective visual vertical (SVV), and cervical and ocular vestibular-evoked myogenic potentials (VEMPs) when considered necessary. Detailed methods of each test have been described previously [17, 18].

MRI and Lesion Analysis

All patients had MRIs to document brainstem or cerebellar lesions. The MRI protocol included diffusion- (DWI), fluid-attenuated inversion recovery- (FLAIR), T1-, and T2-weighted gradient-echo axial imaging, and T1-weighted sagittal imaging using a 3.0- ($n = 35$) or 1.5-T ($n = 33$) unit (Intera; Philips Medical Systems, Best, The Netherlands). Detailed imaging parameters and methods for lesion analysis have been described previously [19]. FLAIR and T1-weighted enhanced images were spatially normalized with SPM 8 (www.fil.ion.ucl.ac.uk/spm/software/spm8). To identify any difference in the lesion location between NMOSD and MS, we analyzed acute lesions on brain MRIs of each patient. Acute lesions were defined by newly developed lesions on T2-weighted images in association with increased signal intensity on FLAIR, or gadolinium-enhancement. Those lesions were carefully delineated and overlapped onto the spatially unbiased atlas template of the cerebellum and brainstem [20]. Using MRIcron (www.mccauslandcenter.sc.edu/mricro/mricron), the overlap images were then obtained for MS and NMOSD using lesion density plots. A voxel-wise statistical analysis of those overlapped lesions was then conducted using the NPM (www.mricro.com/npm). To acquire a subtraction image, we flipped the regions of interest in patients with right-sided lesions and displaced those onto the left side. Likewise, the right-sided lesions in patients with bilateral lesions were also flipped onto the left side.

Statistical Analysis

Statistical analyses were also performed using SPSS (version 18.0; SPSS, Chicago, IL, USA). Nominal variables were compared using χ^2 or Fisher's exact test, and linear-by-linear association. The significance level was set at $p < 0.05$.

All variables with a p value < 0.2 using a univariate analysis were included in the multivariate analysis. Then, all variables with a p value < 0.05 were decided to be significant in the multivariate analysis. All analyses were performed with R release 4.3.3 software.

Results

Clinical Characteristics

The presenting symptoms and clinical and laboratory findings are summarized in Tables 1 and 2. Eighteen patients initially presented the brainstem syndrome (9/42 (21%) in MS and 9/26 (34%) in NMOSD). Twenty-two (22/26, 85%) patients with NMOSD were positive for serum anti-AQP4 antibodies. Patients with NMOSD showed a higher female predominance than

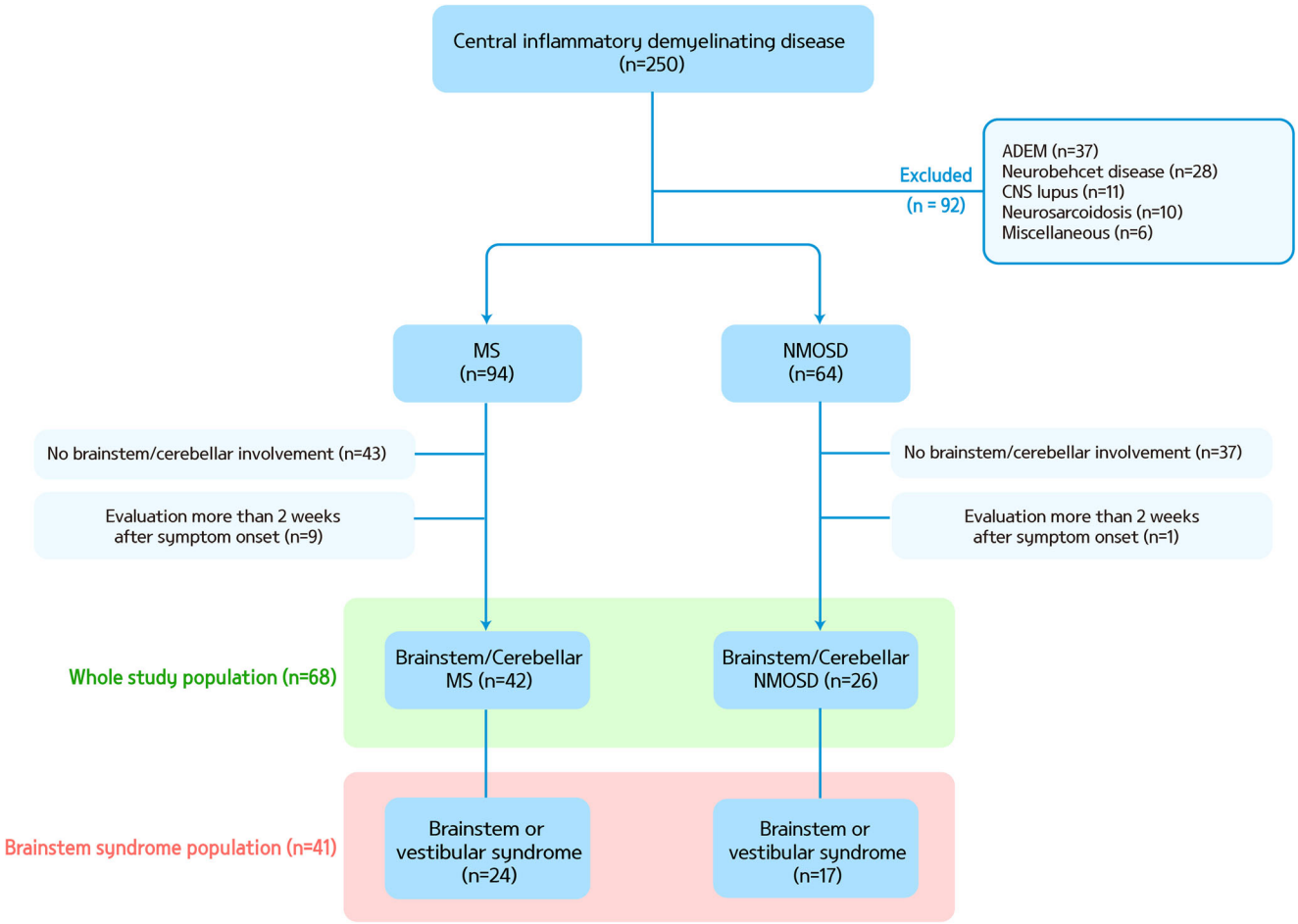

Fig. 1 A flow chart for patient selection. ADEM acute disseminated encephalomyelitis, MS multiple sclerosis, NMOSD neuromyelitis optica spectrum disorder

those with MS (17/25 (68%) vs. 3/23 (13%), $p = 0.003$, Table 1). In addition, intractable nausea/vomiting (13/26 (50%) vs. 7/42 (17%), $p = 0003$) and hiccup (6/26 (23%) vs. 0/42 (0%), $p = 0.001$) were more frequently observed in NMOSD than in MS (Table 2).

Neurotologic Findings

The ocular motor findings are summarized in Table 3. In the whole study population, patients with NMOSD showed abnormal HITs ($p = 0.013$) and horizontal GEN ($p < 0.001$) more

Table 1 Clinical findings in the patients

	MS ($n = 42$)	NMOSD ($n = 26$)	p value
Age, mean ± SD, years	37 ± 12	43 ± 15	0.068
Male/female	17/25	3/23	*0.014*
Age at disease onset, mean ± SD, years	35 ± 12	40 ± 14	0.084
Onset-to-evaluation, median (IQR), days	5 (3–10)	5 (3–7)	0.741
Relapse numbers before presentation	1 (0–3)	1 (0–2)	0.707
EDSS at presentation, median (IQR)	2 (1.5–3)	2 (1.5–4)	0.068
EDSS after 3 months, median (IQR)	1(0–2)	1 (0–3)	0.417
Bilateral lesion (%)	11/42 (26)	16/26 (62)	*0.005*
Lesion size, median (IQR), mL	4.2 (2.2–13.5)	10.7 (3.8–16.4)	0.136
INO (%)	8/42 (19)	3/26 (12)	0.512

EDSS, expanded disability status scale; *INO*, internuclear ophthalmoplegia; *IQR*, interquartile range; *MS*, multiple sclerosis; *NMOSD*, neuromyelitis optica spectrum disorder; *SD*, standard deviation

Values in Italics are with $p < 0.05$

Table 2 Presenting symptoms of the patients

Symptoms	MS (%)	NMOSD (%)	*p* value
Dizziness, vertigo	18/42 (43)	14/26 (54)	0.457
Headache	7/42 (17)	4/26 (15)	≈ 1.000
Intractable nausea/vomiting	7/42 (17)	13/26 (50)	*0.003*
Sensory change	20/42 (48)	13/26 (50)	0.849
Diplopia	10/42 (24)	7/26 (27)	0.773
Motor weakness	13/42 (31)	10/26 (39)	0.525
Limb ataxia	7/42 (17)	7/26 (27)	0.309
Dysarthria	7/42 (17)	7/26 (27)	0.309
Facial palsy	9/42 (21)	2/26 (8)	0.184
Intractable hiccup	0/42 (0)	6/26 (23)	*0.001*
Decreased visual acuity	2/42 (5)	2/26 (8)	0.633
Dysgeusia	4/42 (10)	1/26 (4)	0.642
Mental change	1/42 (2)	0/26 (0)	≈ 1.000
Seizure	1/42 (2)	0/26 (0)	≈ 1.000
Dyspnea	1/42 (2)	0/26 (0)	≈1.000

MS, multiple sclerosis; *NMOSD*, neuromyelitis optica spectrum disorder
Values in Italics are with $p < 0.05$

frequently than those with MS (Table 3, Fig. 2). HITs were abnormal to the lesion side ($n = 2$), to the healthy side ($n = 1$), or in both directions ($n = 2$, including one with a bilateral lesion) in the patients with NMOSD. Meanwhile, HITs were abnormal to the lesion side only in a patient with MS.

Table 3 Ocular motor findings in the patients

	MS (%)	NMOSD (%)	*p* value
Spontaneous nystagmus	15/42 (36)	14/26 (54)	0.142
GEN			
Horizontal	4/42 (10)	13/26 (50)	*< 0.001*
Vertical	3/42 (7)	4/26 (16)	0.411
Rebound nystagmus	5/41 (12)	9/23 (39)	*0.012*
Perverted rebound nystagmus	2/42 (5)	1/26 (4)	≈ 1.000
Abnormal HITs	1/38 (3)	5/19 (26)	*0.013*
Canal paresis	5/22 (23)	4/12 (33)	0.687
HSN	10/40 (25)	5/22 (23)	0.842
Positional nystagmus	8/39 (18)	8/23 (35)	0.135
INO	8/42 (19)	3/26 (12)	0.414
Ocular motor palsy other than INO	10/42 (24)	4/26 (15)	0.404
Cervical VEMPs	10/23 (44)	7/11 (64)	0.271
Ocular VEMPs	8/13 (62)	2/9 (22)	0.099
SVV	12/25 (48)	6/13 (46)	≈ 1.000
OTR			
Head tilt	5/42 (12)	3/26 (12)	≈ 1.000
Skew deviation	5/42 (12)	3/26 (12)	≈ 1.000
Ocular torsion	11/32 (34)	4/11 (36)	0.905

GEN, gaze-evoked nystagmus; *INO*, internuclear ophthalmoplegia; *HITs*, head-impulse tests; *MS*, multiple sclerosis; *NMOSD*, neuromyelitis optica spectrum disorder; *OTR*, ocular tilt reaction; *SVV*, subjective visual vertical; *VEMP*, vestibular-evoked myogenic potentials
Values in Italics are with $p < 0.05$

Forty-one (41/68, 60%) patients presented acute brainstem syndrome, and most (31/41, 76%) of them showed at least one central ocular motor sign, including GEN in either horizontal ($n = 17$) or vertical ($n = 7$) direction, SN with negative HITs ($n = 15$), skew deviation ($n = 8$), pure vertical ($n = 4$), dissociated torsional-vertical SN ($n = 3$), or perverted downbeat HSN ($n = 4$).

Logistic regression analysis showed that bilaterality of the lesions ($p = 0.007$) and horizontal GEN ($p = 0.024$) were more frequently associated with NMOSD than with MS in the whole study population (Table 4). In patients with acute brainstem syndrome, however, only horizontal GEN was more frequent in NMOSD than in MS ($p = 0.020$, Table 4).

Follow-up analyses of ocular motor findings were conducted in 21 patients (nine with NMOSD and 12 with MS) within a median of 8 weeks after the initial evaluation (interquartile range = 3–12 weeks). Most patients showed a partial ($n = 12$) or complete ($n = 5$) recovery of the ocular motor findings along with a clinical recovery. Only a small number of patients showed no improvement ($n = 3$) or aggravation ($n = 1$). The proportion of patients with a recovery did not differ between the patients with MS and NMOSD (linear-by-linear association, $p = 0.568$).

Clinico-Anatomic Correlation

About a half of patients (32/68, 47%) had responsible lesions restricted to the brainstem or cerebellum while the remaining 36 patients also had concurrent lesions involving the cerebrum (28/68, 41%), spinal cord (9/68, 13%), or optic nerve (1/68, 1%). Only three patients (3/68, 4%) had a cerebellar involvement. Using the voxel-wise subtraction analysis, the lesions specific for NMOSD were overlapped in the medial vestibular nucleus (MVN) and nucleus prepositus hypoglossi (NPH) at the pontomedullary junction (Figs. 3 and 4).

Discussion

Our findings can be summarized as follows: (1) horizontal GEN is more frequently observed in NMOSD than in MS. (2) Compared to MS, NMOSD is more likely to involve the MVN and NPH on both sides.

The shape, location, and symmetry of the lesions may differ between MS and NMOSD. MS usually presents with periventricular and well-defined ovoid lesions while the lesions in NMOSD are more likely distributed along the peri-ependymal regions on both sides with the

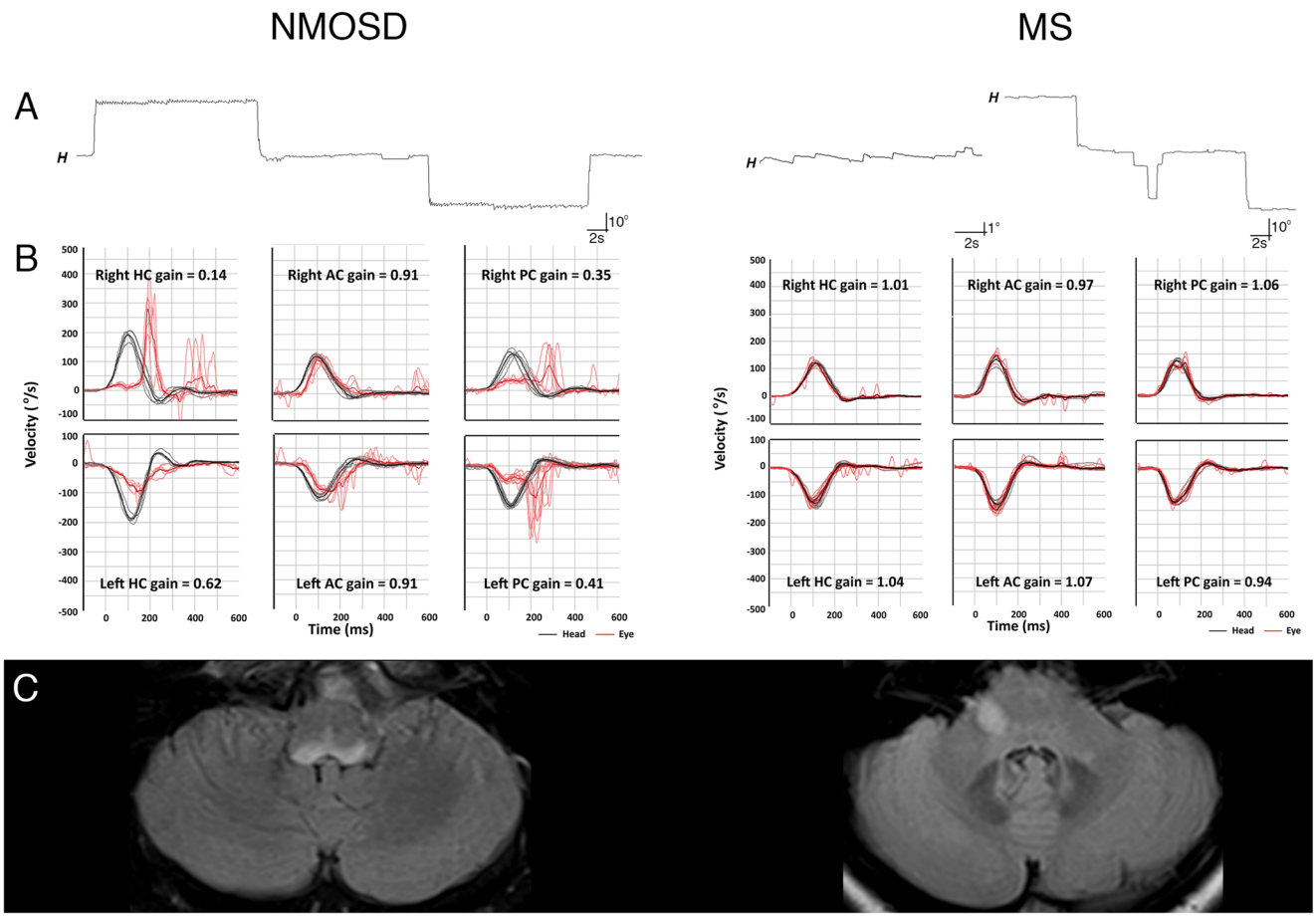

Fig. 2 Representative cases of neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS). **A.** A patient with NMOSD shows gaze-evoked nystagmus and rebound nystagmus during lateral gazes while the other patient with MS shows spontaneous nystagmus beating to the right (1°/s) without a change in direction during lateral gazes. **B** The patient with NMOSD shows decreased gains of the vestibulo-ocular reflex and corrective catch-up saccades for horizontal (HC) and posterior semicircular canals (PC) on both sides. In contrast, the patient with MS shows normal head impulse tests. **C** Fluid-attenuated inversion recovery MRIs show a bilateral lesion in the dorsal portion of the medulla in the patient with NMOSD. The patient with MS has a lesion involving the anterolateral portion of the caudal pons. AC anterior canal, H horizontal position of the left eye; in **A**, upward deflection indicates rightward eye motion

pattern of vasogenic edema on DWI [2, 6]. The lesions in NMOSD are characteristically distributed in the sites of high AQP4 protein expression [2]. While MS is more likely to involve the pons, NMOSD more commonly affect the medulla or cervicomedullary junction [2, 21]. In addition, NMOSD almost always involves the dorsal portion while MS tends to involve both the ventral and dorsal parts almost equally [21, 22]. However, the differentiation of NMOSD from MS based on MRI findings may be misleading since 9~13% of NMOSD lesions also meet the MS criterion of dissemination in space [2].

Various forms of abnormal eye movements have been reported in MS, including spontaneous downbeat nystagmus [23, 24], pendular nystagmus [25], GEN [26], periodic alternating nystagmus [27], central positional nystagmus [26], internuclear ophthalmoplegia [28], and impaired suppression of the vestibulo-ocular reflex [29]. Our study confirms the previous finding that about 16% of MS patients may show GEN [26]. Patients with NMOSD also showed various ocular motor findings that comprise convergence-retraction nystagmus [30], downbeat nystagmus [30], upbeat nystagmus [31], and opsoclonus [31]. Although, horizontal GEN may be observed both in MS and NMOSD, our study showed that patients with NMOSD are more likely to have horizontal GEN.

The clinical presentation of NMOSD and MS may differ in many aspects. Usually, NMOSD has a similar prevalence worldwide [32], with a female predominance and an older onset compared to MS [33]. In addition, the prognosis is generally worse in NMOSD, which more frequently results in permanent visual and motor disability, or mortality [34]. Besides, painful tonic spasm [35] and neuropathic pruritus [36] are more frequent in myelitis due to NMOSD.

Intractable hiccup and nausea/vomiting have been considered to be the features that may distinguish NMOSD from MS, especially when the area postrema

Table 4 Prediction of NMOSD compared to MS

	Whole study population ($n = 68$)				Brainstem syndrome population ($n = 41$)			
	Unadjusted OR (95% CI)	Age and sex adjusted OR (95% CI)	Current model 1*	p value for *	Unadjusted OR (95% CI)	Age and sex adjusted OR (95% CI)	Current model 1*	p value for *
Intractable nausea/vomiting	5.00 (1.64, 15.29)	1.05 (1.00, 1.09)	2.58 (0.52, 12.80)	0.245	4.29 (1.13, 16.31)	6.61 (1.38, 31.77)	16.17 (0.74, 352.07)	0.077
hGEN	9.50 (2.63, 34.36)	18.8 (3.4, 104.57)	10.39 (1.1, 98.40)	*0.041*	16.3 (3.8, 88.5)	60.73 (4.87, 757.27)	44.15 (1.94, 1003.14)	*0.017*
INO	1.80 (0.43, 7.53)	0.33 (0.71, 1.53)	–	–	0.52 (0.11, 2.39)	0.41 (0.08, 2.02)	–	–
Abnormal HITs	12.33 (1.33, 114.62)	8.49 (0.80, 90.70)	10.37 (0.69, 155.79)	0.091	10.50 (1.01, 108.76)	7.90 (0.69, 89.93)	16.07 (0.33, 795.39)	0.163
Bilateral lesion	4.51 (1.58, 12.85)	5.66 (1.73, 18.51)	9.30 (1.65, 52.46)	*0.012*	3.5 (0.9, 12.8)	3.97 (0.98, 16.07)	1.56 (0.12, 19.69)	0.730

*Current model 1 is adjusted for factors having p value less than 0.2 (including intractable nausea/vomiting, hGEN, abnormal HITs, bilateral lesion, in addition to age and sex)

† Hiccup could not be included in logistic regression due to its null incidence in MS

hGEN, horizontal gaze-evoked nystagmus; *HITs*, head-impulse tests; *INO*, internuclear ophthalmoplegia; *MS*, multiple sclerosis; *NMOSD*, neuromyelitis optica spectrum disorder; *OR*, odds ratio

Values in Italics are with $p < 0.05$

and the nucleus tractus solitarius are involved [11]. The vestibular nucleus and NPH reside in the rostral medulla and caudal pons, adjacent to the fourth ventricle [8]. As NMOSD has a higher chance of involving the neural structures adjacent to the 4th ventricle, the MVN-NPH complex may have been affected more frequently to present horizontal GEN and rebound nystagmus [8].

Lesions affecting the neural integrator interrupt holding the eyes in the eccentric positions, and give rise to GEN [37]. A characteristic feature of lesions involving the MVN and NPH is combined peripheral and central vestibular dysfunction [8, 10]. Horizontal-torsional spontaneous nystagmus beating away from the lesion side, positive HITs to the lesion side and ipsilesional caloric paresis are all suggestive of unilateral peripheral vestibulopathy. In contrast to the lesions involving the vestibular nerve or fascicles, those involving the MVN give rise to positive HITs in both horizontal directions in addition to horizontal GEN [8]. Medial to the MVN, the NPH lies from the rostral medulla to caudal pons

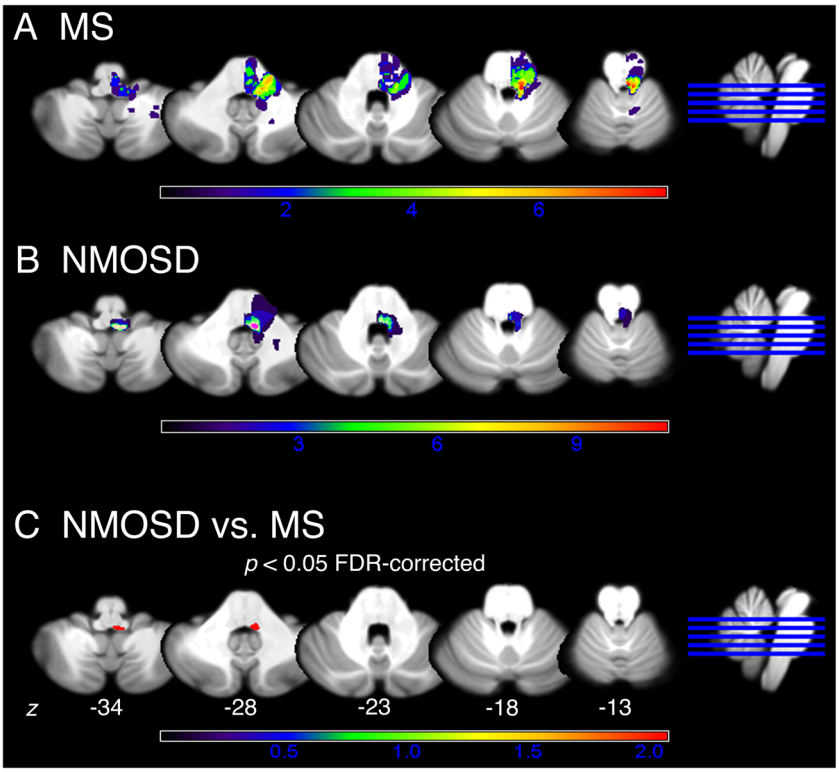

Fig. 3 Probabilistic lesion mapping analysis. The overlay plots (**A**, **B**) and subtraction images (**C**) show that the medial vestibular nucleus and nucleus prepositus hypoglossi are frequently involved in patients with neuromyelitis optica spectrum disorder (NMOSD). For subtraction analysis (**C**), the overlapping lesions in multiple sclerosis (MS) patients (**A**) were subtracted from those of NMOSD patients (**B**). Regions in red ($p < 0.05$ FDR-corrected) indicate the regions damaged more frequently in NMOSD patients. z indicates the Talairach coordinates

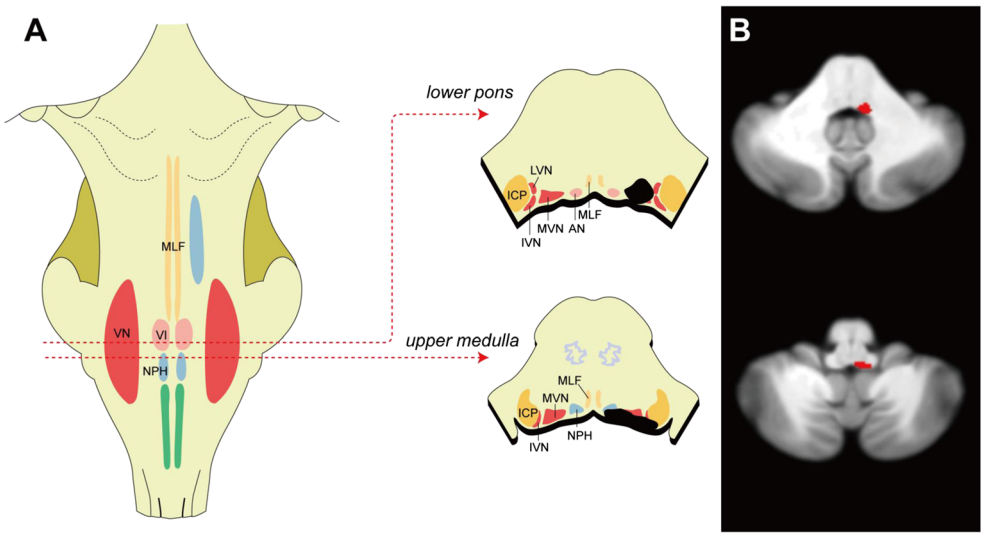

Fig. 4 **A.** Schematic illustration of the neural substrates involved frequently in our patients with neuromyelitis optica spectrum disorder. The lesions are marked in black. **B.** The probabilistic lesion mapping analyses. AN abducens nucleus (VI), ICP inferior cerebellar peduncle, IVN inferior vestibular nucleus, LVN lateral vestibular nucleus, MLF medial longitudinal fasciculus, MVN medial vestibular nucleus, NPH nucleus prepositus hypoglossi

between the hypoglossal and abducens nuclei [38]. The inferior olive receives an inhibitory projection from NPHs on both sides. As the projections are stronger from the contralateral NPH, lesions affecting the NPH would produce contralateral vestibular inhibition to mimic a lesion involving the contralateral MVN [8].

Patients with anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibody may present with intractable nausea/vomiting, diplopia, and internuclear ophthalmoplegia, and thus may mimic NMOSD [39]. Indeed, the brainstem can be involved in about 30% of anti-MOG autoantibody-associated demyelinating disease [39]. In this study, we did not measure anti-MOG antibody, but the ocular motor features of anti-MOG autoantibody-associated demyelinating disease should be defined further in comparison to those of NMOSD and MS.

Of interest, one-fourth to one-third of our patients had a brainstem syndrome as the initial presentation of MS or NMOSD. Indeed, nearly 20% of NMOSD patients have brain lesions without involving the optic nerve or spinal cord [40]. Accordingly, differentiation of NMOSD from MS may not be apparent without further attacks involving the optic nerve or spinal cord. Along with the characteristic bilateral lesions on MRIs, our study implicates that analyses of ocular motor findings can aid in differentiation of NMOSD from MS during the early stage of the diseases.

Author Contributions Dr. Lee analyzed and interpreted the data, and wrote the manuscript.

Drs. H.J. Kim, J.Y. Choi, and J.H. Choi analyzed and interpreted the data, and revised the manuscript.

Dr. J.S. Kim designed and conceptualized the study, interpreted the data, and revised the manuscript.

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Compliance with Ethical Standards

Conflict of Interest S.U. Lee, H.J. Kim, J.Y. Choi, and J.H. Choi report no disclosure.

J.S. Kim serves as an Associate Editor of Frontiers in Neuro-otology and on the editorial boards of the Journal of Clinical Neurology, Frontiers in Neuro-ophthalmology, Journal of Neuro-ophthalmology, Journal of Vestibular Research, Journal of Neurology, and Medicine, and received research support from SK Chemicals, Co. Ltd.

Ethical Standard This study followed the tenets of the Declaration of Helsinki and was performed according to the guidelines of Institutional Review Board of Seoul National University Bundang Hospital (B-1810-497-102) and Pusan National University Yangsan Hospital (05-2018-127).

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