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Comparison of psychiatric disturbances in patients with multiple sclerosis and neuromyelitis optica

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Abstract

Although both multiple sclerosis (MS) and neuromyelitis optica (NMO) are demyelinating diseases, their psychiatric disturbances may differ given differences in the neurological manifestations. We used subjective and objective measurements to compare the psychiatric disturbances in patients with MS and NMO.

Psychiatric disturbances were assessed in 24 MS and 35 NMO patients using the Beck Hopelessness Scale, Symptom Checklist-95 and the brief version of World Health Organization Quality of Life. Personality was assessed using the Big Five Inventory-10. Disease-related function was assessed using the Fatigue Severity Scale, Short-Form McGill Pain Questionnaire, and the Global Assessment of Function. Positivity offset (PO) and negativity bias (NB) and heart rate variability (HRV) were measured using a modified implicit affect test and photoplethysmograph, respectively. Data were analyzed using analysis of covariance with age and sex as covariates.

MS patients had higher levels of depression, anxiety, panic attacks, obsessive–compulsiveness, aggression, paranoia, interpersonal sensitivity, self-regulation problems, stress vulnerability, and lower psychological quality of life (QOL) compared with NMO patients. The PO and NB and HRV values were not significantly different between groups. However, NMO patients had lower QOL, and higher levels of hopelessness, suicidality, and fatigue than the normal range. Disease duration was associated with hopelessness in NMO patients and with several psychiatric disturbances, but not hopelessness, in MS patients.

Subjective psychiatric disturbances were more severe in patients with MS than in those with NMO, whereas PO and NB and HRV in patients with NMO were comparable with those of MS patients. Our findings highlight the need for different clinical approaches to assess and treat psychiatric disturbances in patients with MS and NMO.

Abbreviations: ARR = annualized relapse rate, BFI-K-10 = Korean version of the Big Five Inventory-10, BHS = Beck Hopelessness Scale, CNS = central nervous system, EDSS = Expanded Disability Status Scale, FSS = Fatigue Severity Scale, GAF = Global Assessment of Functioning, HRV = heart rate variability, MS = multiple sclerosis, NB = negativity bias, NMO = neuromyelitis optica, OCD = obsessive–compulsive disorder, PO = Positivity offset, PPG = photoplethysmography, QOL = quality of life, SCL-95 = Korean Symptom Checklist-95, SF-MPQ = Short-Form McGill Pain Questionnaire, WHOQOL-BREF = World Health Organization Quality of Life-BREF.

Keywords: heart rate variability, mental disorders, multiple sclerosis, neuromyelitis optica, quality of life

1. Introduction

Multiple sclerosis (MS) and neuromyelitis optica (NMO) are chronic idiopathic inflammatory demyelinating diseases of the central nervous system (CNS) that occur throughout the world. Although MS and NMO have overlapping manifestations, including a chronic relapsing course and CNS demyelination, recent clinical, radiological, histopathological, and immunologic studies have shown that the diseases can be distinguished.[1]

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MS is characterized by the demyelination of CNS white matter disseminated in time and spaces. MS is one of the most common chronic neurological disorders in young adults, affecting an estimated 1.1 million patients worldwide.[2] In Korea, the crude prevalence of MS is 3.5 to 3.6/100,000 individuals.[3] Typical neurological complications in the early stages of MS include sensory disturbances, diplopia, unilateral optic neuritis, limb weakness, and gait ataxia. NMO selectively involves the optic nerves and spinal cord, but typically spares the brain. NMO is considered to be a more serious disease than MS because the symptoms, including loss of vision and gait function, are more disabling and frequently require immunosuppressant therapy.[4].

In addition to neurological deficits, MS and NMO patients may experience psychiatric symptoms such as depression, anxiety, pain, and lower quality of life (QOL),[4–6] which may be the result of direct demyelination of CNS structures and the unpredictable and progressive nature of the clinical course. According to previous studies, about half of patients with MS experience depression,[7] and one-third have clinically significant anxiety symptoms.[8] Patients with NMO have a high prevalence of moderate-to-severe depression comparable to that of patients with MS.[9]

Although research interest in the psychiatric disturbances associated with MS and NMO has grown in recent years, few patients with MS and NMO receive sufficient treatment.[9] Furthermore, despite different psychiatric symptom profiles, the clinical approaches for patients with MS and NMO are virtually the same. Given that these patients are generally treated in the same clinics, an understanding of the characteristics and psychiatric disturbances specific to MS and NMO is necessary to provide the most effective treatment for each disease.

However, the few comprehensive studies of psychiatric disturbances in patients with MS and NMO using measures other than subjective reports have yielded inconsistent findings. A recent study in patients with NMO found a high prevalence and severity of depression comparable to that of patients with MS.[10] Moreover, recurrent depression and suicidality was found to be more common in patients with NMO than in those with MS.[11] Another study found no significant difference in QOL and depression between patients with MS and NMO.[4]

We compared psychiatric disturbances in patients with MS and NMO using the objective measurements of positivity offset (PO) and negative bias (NB) and heart rate variability (HRV) together with self-report questionnaires. PO is the tendency to respond with more positive than negative affect to mild emotional stimuli, whereas NB is the tendency to respond more strongly to very negative stimuli than to matched positive stimuli.[12] PO and NB are independent of personality trait, stable over time, generalizable to various stimuli, and a useful predictor of behavioral therapy outcome in depressed patients.[13] HRV, the change in the time interval between successive heartbeats, is an index of parasympathetic tone, and is associated with various psychophysiological traits including cognition, emotions, and social behaviors[14]. Given the non-invasive nature, low-cost, and ease of data collection, HRV is an accessible and feasible measure of physiological parameters for various neuropsychiatric disorders.[15]

We compared the extent of psychiatric disturbances in patients with MS and NMO using subjective and objective assessment techniques. We hypothesized that patients with NMO would report higher levels of depression, anxiety, hopelessness, and lower QOL, and show lower PO, higher NB, and reduced HRV compared with MS patients. Furthermore, we predicted that longer disease duration would be associated with severe psychiatric disturbances in MS and NMO patients.

2. Methods

2.1. Participants and clinical assessments

The study included 24 patients with MS and 35 with NMO recruited from the outpatient clinics of the Neurology Department of Seoul National University Hospital (SNUH, Seoul, Republic of Korea) and online and offline advertisements through the Korean Multiple Sclerosis Society between August 2017 and April 2019. Patients between the ages of 19 and 80 years diagnosed with MS or NMO according to the revised McDonald criteria[16] or international consensus criteria of Wingerchuk et al,[1] respectively, were included in the study. Individuals who did not provide consent for participation or were unable to understand and complete the questionnaires without help were excluded from the study. Our study was approved by the Institutional Review Board of SNUH.

Neurological impairment was assessed using the Expanded Disability Status Scale (EDSS)[17] administered by the treating neurologist at enrollment. The EDSS is used to measure disease progression and neurological function in both MS and NMO patients. Medical data including, age at onset, disease duration, and annualized relapse rate (ARR), were obtained from the electrical medical records (EMR) of the participants. Brain and spinal cord magnetic resonance imaging (MRI) scans acquired within 1 year of enrollment were anonymized and assessed by an independent neurologist. The EMR data and MRI scans of 1 MS patient were inaccessible because he was not a registered patient of SNUH.

2.2. Measures

2.2.1. Subjective measures of psychiatric disturbances. Self-report questionnaires were used to assess subjective psychiatric disturbances. The Beck Hopelessness Scale (BHS)[18] is a predictor of suicidal attempt and indicator of cognitive-behavioral therapy outcome in patients with depressive disorder. BHS scores higher than 4 indicate high levels of hopelessness. We used the Korean Symptom Checklist-95 (SCL-95) to screen for general psychiatric symptoms.[19] The SCL-95 is designed to screen individuals at high risk of major clinical psychiatric disorders based on the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders. The SCL-95 was validated using a large Korean sample and has high internal consistency and test-retest reliability. SCL-95 scores higher than 60 indicate high risk for that subscale. Additionally, the Korean version of the World Health Organization Quality of Life-BREF (WHOQOL-BREF)[20] was used to assess QOL. The WHOQOL-BREF, which is an abbreviated version of the WHOQOL-100, consists of 4 domains (physical, psychological, social relationships, and environmental) and the total score is calculated as the mean of all of the domains. Higher scores indicate better QOL and a total score of less than 60 indicates poor QOL.[21]

2.2.2. Personality and disease-related function. Self-report questionnaires were used to assess factors that may affect psychiatric disturbances. The Korean version of the Big Five Inventory-10 (BFI-K-10)[22] was used to assess underlying personality traits according to 5 personality factors (extraversion, agreeableness, conscientiousness, neuroticism, and openness).

Fatigue was evaluated using the Fatigue Severity Scale (FSS)[23] which has been validated in patients with MS.[24] Fatigue was defined as a score of 4 or more. The Short-Form McGill Pain Questionnaire (SF-MPQ)[25] was used to assess pain. The Global Assessment of Functioning (GAF) scale[26] was used to measure global function.

2.2.3. PO and NB. PO and NB were assessed using a modified implicit affect task[12] a computer-based task in which participants are instructed to make valance ratings while viewing color pictures of emotional images obtained from the International Affective Picture System (IAPS).[27]

The images were divided into 3 groups of 18 images each,[i] based on their normative valence ratings: negative, positive and neutral.[28] Participants were told they would see images with varying emotional content and were instructed to focus on each picture for the duration of the presentation time. Images were presented in a pseudorandom order (counterbalanced for participants) for 4 seconds with a fixation period of 0.5 seconds before and after the presentation.[13] During the fixation period, participants were instructed to look at the fixation point in the center of the screen, which was then replaced by an image. Participants rated the valance as positive or negative using a 5-point Likert scale on a 5×5 evaluative space grid with positivity measured on the x-axis and negativity on the y-axis ranging from (0) not at all to (4) = extremely positive/negative. Then participants were asked to rate the level of arousal evoked by the image on a 9-point Likert scale ranging from (1) least arousing to (9) most arousing.[12] No limits were placed on the evaluation time.

2.2.4. HRV. The participants were instructed to avoid strenuous exercise 1 hour before and alcohol, caffeine, and smoking 12 hour before the measurement of HRV. Participants with cardiopulmonary disease were excluded from the analysis. Participants were seated in a quiet room, and a finger photoplethysmography (PPG) sensor was placed on the nail of their right fifth finger. The PPG uses a small light to detect blood volume changes in the microvascular tissue. PPG recordings were conducted for 5-minute-at-rest and data were sampled at 1000 Hz to assess HRV. The 5-minute PPG recording is a cost-effective technique for the assessment of HRV with accuracy comparable to electrocardiogram recordings in the resting state,[29] despite limitations including inability to detect respiration and the time frame not appropriate for measuring very low frequency (<0.04 Hz) components of the spectral band.[30] A tachogram was obtained by identifying the systolic peaks of the PPG signal and measuring the time difference between successive peaks. The tachogram was exported to Kubios HRV software (version 3.1.0; University of Kuopio, Kuopio, Finland) for the analysis of HRV. Spectral analysis was done with the Fast Fourier transform, and all HRV measures were generated according to the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[31]

[i] IAPS stimuli numbers: 8190, 9090, 7170, 5626, 1540, 4490, 7002, 4660, 7035, 7030, 3000, 7340, 7330, 7830, 2170, 2091, 7190, 2040, 2190, 8230, 9500, 8501, 3120, 7430, 7360, 7235, 9571, 7233, 7040, 9630, 4640, 5530, 2150, 9830, 2750, 7217, 1920, 7025, 6230, 4599, 5600, 9390, 7010, 9570, 5820, 9600, 6150, 7050, 1274, 7500, 9560, 9400, 7390, 7140.

2.3. Statistical analyses

The demographic and clinical characteristics of the patients with MS and NMO were compared using descriptive statistics, Student *t* test, and the Mann–Whitney *U* test, as appropriate. The subjective psychiatric disturbances, PO and NB and HRV were compared between groups using analysis of covariance (ANCOVA), with age and sex as covariates. *P* values $< .05$ were considered to indicate statistical significance. Partial correlation analyses were performed to assess the association between disease duration and subjective psychiatric disturbances controlling for age and sex. All statistical tests were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

The demographic and clinical data of the MS and NMO patients are shown in Table 1. The mean age and age at onset were higher in the patients with NMO than in those with MS (both, $P < .001$); however, the sex ratio did not differ between groups ($P = .198$). Although 8.3% of the patients with MS and 17.1% of those with NMO had been diagnosed previously with psychiatric disorders, including depression, panic attacks, and insomnia, no differences in psychiatric comorbidity were found between the groups ($P = .453$). Similarly, the clinical variables, including the EDSS and ARR findings, were not significantly different between the MS and NMO groups. Although supratentorial involvement was less frequent in patients with NMO than in those with MS, 14 (40.0%) NMO patients had supratentorial lesions ($P < .001$). Although no significant differences in personality traits, fatigue, pain, or GAF scores were found between groups, the level of fatigue in both groups was above the normal range.

3.2. Comparison of subjective psychiatric disturbances in patients with MS and NMO

The patients with MS had significantly higher levels of depression, anxiety, panic, obsessive–compulsive disorder (OCD), obsessive–compulsive personality trait, obsessive–compulsiveness, aggression, paranoia, addiction, interpersonal sensitivity, self-regulation problems, and stress vulnerability compared with NMO patients after controlling for age and sex (Table 2). Moreover, patients in the MS group reported lower psychological QOL than those in the NMO group. Although the level of hopelessness reported by NMO patients did not differ from that of MS patients, their QOL was lower and the levels of hopelessness and suicidality was higher than the normal range.

3.3. Comparison of the objective measures of psychiatric disturbances in patients with MS and NMO

3.3.1. PO and NB. No significant differences in PO and NB were found between the MS and NMO groups after controlling for age and sex ($P = .206$ and $P = .899$, respectively; Table 3).

3.3.2. HRV. The comparison of HRV between the MS and NMO groups revealed no significant differences in the time domain and frequency domain parameters after controlling for age and sex (Table 4).

Table 1

Patient demographic and clinical characteristics.

	MS ($n=24$)	NMO ($n=35$)	*P* value
Demographic variables[†]			
Sex, male (%)	7 (29.2)	5 (14.3)	.198
Age (years)	32.13 ± 11.82	48.97 ± 13.36	<.001[*]
Education (years)	14.75 ± 2.58	13.57 ± 3.16	.135
Marital status, married (%)	6 (25.0)	25 (71.4)	.001[*]
Religion, religious (%)	15 (62.5)	24 (68.6)	.780
Alcohol consumption, yes (%)	13 (54.2)	5 (14.3)	.002[*]
Smoking, yes (%)	8 (33.3)	0 (0.0)	<.001[*]
BMI (kg/m2)	21.72 ± 2.60	22.45 ± 4.05	.709
Clinical variables[†]			
Age at onset (years)	29.49 ± 12.18	42.18 ± 14.60	<.001[*]
Duration of disease (months)	40.68 ± 43.94	81.65 ± 111.32	.055
ARR (/years)	1.58 ± 1.84	1.94 ± 2.49	.426
EDSS	2.09 ± 1.71	2.30 ± 2.16	.559
Currently in acute relapse phase (%)	1 (4.2)	1 (2.9)	1.000
Brain (Supratentorial) lesion (%)[§]	23 (100.0)	14 (40.0)	<.001[*]
Brain (Infratentorial) lesion (%)[§]	8 (34.8)	11 (31.4)	1.000
Spinal cord lesion (%)[§]	12 (52.2)	29 (82.9)	.018[*]
Optic nerve lesion (%)[§]	9 (39.1)	14 (40.0)	1.000
Medical comorbidity (%)	12 (50.0)	17 (48.6)	1.000
Psychiatric comorbidity (%)	2 (8.3)	6 (17.1)	.453
Family history of depression (%)	4 (16.7)	10 (28.6)	.361
Personality and disease-related function[‡]			
Big Five Inventory (BFI-K-10)			
Extraversion	5.21 ± 1.44	5.31 ± 2.00	.915
Agreeableness	6.67 ± 2.01	7.37 ± 1.78	.756
Conscientiousness	6.29 ± 1.55	7.40 ± 1.50	.171
Neuroticism	7.21 ± 1.25	6.20 ± 1.92	.216
Openness	6.71 ± 1.76	6.71 ± 2.27	.725
Fatigue Severity Scale (FSS)	4.45 ± 1.40	4.43 ± 1.39	.438
Short-Form McGill Pain Questionnaire (SF-MPQ)			
Pain rating index	10.75 ± 8.22	15.44 ± 9.81	.223
Sensory subscale	0.92 ± 0.56	1.00 ± 0.73	.833
Affective subscale	0.84 ± 0.77	1.04 ± 0.79	.767
Present pain intensity	1.17 ± 1.20	2.09 ± 1.44	.536
Visual analog scale	4.08 ± 2.83	5.88 ± 2.75	.587
Global Assessment of Functioning (GAF)	78.54 ± 9.61	76.74 ± 9.43	.232

Data are *n* (%) or mean ± standard deviation values.

[*] $P < .05$.

[†] *P* values for continuous variables are from t tests and from Fisher's exact test on categorical variables.

[‡] *P* values from analyses of covariance, adjusting for age and sex.

[§] Brain imaging data from one patient with MS was missing.

ARR = annualized relapse rates, BMI = body mass index, EDSS = expanded disability status scale, MS = multiple sclerosis, NMO = neuromyelitis optica.

3.4. Association between disease duration and subjective psychiatric disturbances

The coefficients of partial correlation between disease duration and subjective psychiatric disturbances after controlling for age and sex are shown in Table 5. Longer disease duration was correlated with higher levels of hopelessness, agoraphobia, and somatization in the patients with NMO, whereas in the patients with MS, longer disease duration was associated with higher levels of depression, anxiety, panic attacks, phobic anxiety, OCD, obsessive-compulsiveness, posttraumatic stress disorder, somatization, paranoia, schizophrenia, suicide, interpersonal sensitivity, and stress vulnerability.

4. Discussion

Our findings showed that subjective psychiatric disturbances were more common in patients with MS than in those with NMO despite similar levels of disease severity. In contrast, PO and NB and HRV value were not significantly different between groups. Although several previous studies conducted in Western countries have compared psychiatric disturbances in patients with MS and NMO, to our knowledge, our study is the first to compare subjective and objective measures of psychiatric disturbances.

We confirmed that patients with MS had higher levels of depression and anxiety than those with NMO, despite no significant differences in personality traits. This finding is not consistent with previous studies that found no significant differences in the prevalence and patterns of depression and anxiety between MS and NMO patients.[9,32] In general, the brain areas associated with organic depression, such as the prefrontal area, limbic system, and hippocampus, are spared in patients with NMO.[33] Several studies have identified cortical gray matter lesions specific to MS,[34] and gray matter damage is

Table 2

Comparison of subjective psychiatric disturbances in patients with MS and NMO after controlling for age and sex.

	MS ($n=24$)	NMO ($n=35$)	*P* value[†]
Beck Hopelessness Scale (BHS)	8.50 ± 5.98	7.17 ± 6.09	.057
Symptom Checklist-95 (SCL-95)			
Depression	62.04 ± 14.51	58.23 ± 12.62	.040*
Anxiety	61.96 ± 13.74	56.97 ± 12.98	.023*
Panic attack	58.04 ± 19.35	51.40 ± 12.94	.049*
Agoraphobia	56.50 ± 15.09	55.74 ± 14.70	.549
Phobic anxiety	57.46 ± 16.57	54.26 ± 12.40	.216
Obsession–compulsive disorder	57.25 ± 12.26	51.34 ± 12.19	.008*
Obsessive–compulsive personality trait	55.75 ± 10.35	47.66 ± 9.96	<.001*
Obsessive–compulsiveness	56.63 ± 1088	49.60 ± 10.58	.002*
Posttraumatic stress disorder	55.29 ± 15.30	52.91 ± 11.21	.302
Aggression	56.08 ± 13.62	50.09 ± 9.42	.009*
Somatization	56.63 ± 12.59	57.77 ± 11.96	.295
Manic episode	53.13 ± 10.51	50.60 ± 9.33	.668
Paranoia	54.75 ± 16.37	49.23 ± 9.71	.042*
Schizophrenia	55.83 ± 13.51	50.83 ± 11.12	.072
Suicide	60.25 ± 16.66	65.34 ± 63.73	.782
Addiction	53.00 ± 11.35	46.31 ± 1.61	.008*
Sleep problem	56.29 ± 11.47	57.34 ± 12.76	.361
Interpersonal sensitivity	60.08 ± 12.96	54.69 ± 11.42	.030*
Self-regulation problems	59.75 ± 13.14	53.40 ± 11.06	.002*
Stress vulnerability	60.25 ± 12.88	54.40 ± 10.94	.009*
WHO Quality of Life-BREF (WHOQOL-BREF)			
Physical health	43.67 ± 16.57	41.09 ± 18.83	.641
Psychological	37.29 ± 14.28	46.06 ± 17.79	.024*
Social relationships	54.75 ± 15.69	55.71 ± 18.73	.100
Environment	49.88 ± 12.40	50.46 ± 18.84	.121
Total score	46.40 ± 11.21	48.43 ± 14.37	.555

Data are mean ± standard deviation values.
* $P < .05$.
† Analyses of covariance.
MS = multiple sclerosis, NMO = neuromyelitis optica.

correlated with depression in MS patients.[35] Furthermore, our finding that the mean suicide and hopelessness scores in patients with NMO were above normal levels suggests that the perceived mood of these patients did not reflect their actual emotional state.

Our finding that the psychological domain of the WHOQOL-BREF was lower in the patients with MS than in those with NMO is consistent with that of previous studies.[4] Nevertheless, the mean total score of the WHOQOL-BREF in our study revealed poor QOL both in MS and NMO patients. Given that depression and fatigue are associated with poor QOL in both diseases,[5,36] the lower QOL in MS patients may be attributed to higher levels of depression and fatigue compared with NMO patients.

Our screening for major psychiatric disorders revealed that patients with MS had a higher prevalence of obsessive–compulsive disturbances than those with NMO. A previous small cross-sectional study found that the prevalence of OCD in patients with MS (16.1%) was significantly higher than that of the general population.[37] The functional disconnections between the cortical–cortical and/or cortical–subcortical brain regions and brain-white matter abnormalities that occur in MS may contribute to the pathogenesis of OCD.[38–40] Depression has received more attention than OCD in clinical practice; however, given that OCD itself is associated with a high risk of suicidality, and depression comorbid with OCD increases the risk of suicidal attempts,[41] more attention should be given to screening for OCD in patients with MS.

Table 3

Comparison of positivity offset and negativity bias in MS and NMO patients, after controlling for age and sex.

	MS ($n=24$)	NMO ($n=35$)	*P* value*
Positivity offset	0.58 ± 0.87	0.87 ± 0.96	.206
Negativity bias	0.08 ± 0.60	0.11 ± 0.71	.899

Data are mean ± SD values.
* Analyses of covariance.
MS = multiple sclerosis, NMO = neuromyelitis optica, SD = standard deviation.

Fatigue is a common symptom of MS and NMO and, while patients in both groups reported pathological levels of fatigue, the mean FSS scores were not significantly different between groups. A previous study found that while the psychosocial dimension of fatigue was more severe in MS than in NMO patients, no differences were observed in the other dimensions.[4] The fatigue experienced by patients with MS and NMO may be a consequence of depression, which is common in both conditions, or a symptom of the diseases *per se*.[42]

While the subjective assessments of psychiatric disturbances revealed several differences between patients with MS and NMO, the findings of the objective tests were not significantly different between groups. Although several previous studies have compared HRV in patients with MS and healthy controls, the

Table 4

Comparison of heart rate variability in patients with MS and NMO after controlling for age and sex.

	MS ($n=21$)[†]	NMO ($n=33$)[†]	*P* value[‡]
Mean heart rate (beats per minute)	55.17 ± 15.19	57.37 ± 14.02	.554
Time domain parameters			
SDRR (ms)	137.33 ± 110.77	102.11 ± 91.62	.978
RMSSD (ms)	174.54 ± 130.41	140.91 ± 114.83	.992
pNN50 (%)	53.55 ± 36.35	48.81 ± 35.73	.541
Frequency domain parameters			
Total power (ms^2)	26538.45 ± 42090.82	13301.30 ± 24993.99	.710
VLF, absolute power (ms^2)	1654.86 ± 2993.26	842.58 ± 2224.74	.393
LF, absolute power (ms^2)	14954.22 ± 25071.95	6447.36 ± 12320.76	.536
HF, absolute power (ms^2)	9899.60 ± 15897.02	5986.89 ± 11125.84	.944
VLF, relative power (%)[*]	8.73 ± 7.84	7.13 ± 5.53	.114
LF, relative power (%)[*]	54.53 ± 18.58	49.34 ± 20.65	.636
VLF, relative power (%)[*]	36.56 ± 21.04	43.31 ± 23.14	.387
LF/HF ratio	4.35 ± 8.25	3.63 ± 9.71	.961

Data are mean ± SD values.

[*] Relative power was calculated by absolute power of each frequency band over total power.

[†] Data from 3 MS patients and 2 NMO patients were missing.

[‡] Analyses of covariance.

HF = high frequency (0.15–0.4 Hz), LF/HF ratio = ratio of LF over HF, LF = low frequency (0.04–0.15 Hz), MS = multiple sclerosis, NMO = neuromyelitis optica, pNN50 = percent of difference between adjacent N-N intervals that are greater than 50 ms, RMSSD = square root of the mean of the sum of the squares of differences between adjacent normal sinus rhythm R-R intervals, SD = standard deviation, SDRR = standard deviation of normal sinus rhythm R–R intervals, VLF=very low frequency (<0.04 Hz).

results were inconsistent.[43–45] Furthermore, no studies have investigated HRV in patients with NMO or assessed affective bias in MS and NMO. Thus, our study is the first to compare HRV and PO and NB in MS and NMO patients.

In our study, the HRV parameters were not significantly different between the MS and NMO groups. Although autonomic dysfunction is more severe in patients with NMO than in those with MS,[46] HRV did not reflect this difference. Moreover, the PO and NB findings were not significantly different between the MS and NMO groups. Although NB is associated with depression, anxiety, and stress,[47] the measure did not differ between the MS and NMO groups despite significant differences in the levels of depression and anxiety. These findings suggest that although the objective measures of psychiatric disturbances are similar in patients with MS and NMO, those with MS report more subjective distress. Higher brain functions involving the perception of affective and cognitive dimensions may be more severely impaired in MS patients with more supratentorial lesions; however, further study with a larger sample size is warranted.

Table 5

The coefficients of partial correlation between disease duration and subjective psychiatric disturbances of MS and NMO patients, after controlling for age and sex.

	MS ($n=24$)	NMO ($n=35$)
Beck Hopelessness Scale (BHS)	0.346	.440[*]
Symptom Checklist-95 (SCL-95)		
Depression	.593[*]	0.191
Anxiety	.589[*]	0.063
Panic attack	.525[*]	0.078
Agoraphobia	.248	.381[*]
Phobic anxiety	.503[*]	0.329
Obsession–compulsive disorder	.452[*]	−0.077
Obsessive–compulsive personality trait	0.009	0.246
Obsessive–compulsiveness	.432[*]	0.065
Posttraumatic stress disorder	.446[*]	0.024
Aggression	0.388	0.165
Somatization	.464[*]	.419[*]
Manic episode	0.283	−0.097
Paranoia	.652[*]	0.259
Schizophrenia	.627[*]	0.007
Suicide	.564[*]	−0.034
Addiction	0.144	0.037
Sleep problem	0.405	0.071
Interpersonal sensitivity	.539[*]	0.059
Self-regulation problems	0.408	−0.001
Stress vulnerability	.538[*]	0.036

[*] Partial correlation coefficients with *P* values < .05.

MS = multiple sclerosis, NMO = neuromyelitis optica.

Our correlational analysis revealed that the associations between subjective psychiatric disturbances and disease duration differed in MS and NMO patients. Several psychiatric symptoms including depression, anxiety, and suicidality were correlated with disease duration in patients with MS, whereas only hopelessness, agoraphobia, and somatization were associated with disease duration in NMO patients. Although disease duration is a readily obtainable clinical parameter associated with psychiatric complications, the findings of previous studies have been inconsistent.[48,49] Somatization is common in patients who are unable to make sense of their own mind and tend to communicate psychological distress through action rather than verbalization.[50] Therefore, rather than communicating psychological distress on self-report questionnaires, NMO patients may only report feelings of hopelessness given the chronic and relapsing course of the disease. This tendency may explain the lower levels of subjective psychiatric disturbances in NMO compared with MS patients despite having similar physiological parameters. These findings suggest that clinicians should pay attention to hopelessness and somatic complaints that deviate from typical clinical manifestations when assessing NMO patients with long disease duration, despite no mention of common psychiatric disturbances such as depression and anxiety. In contrast, long disease duration may be a reliable predictor of increased anxiety, depression, and suicidality in patients with MS.

Taken together, our findings suggest that MS patients have more psychiatric disturbances than NMO patients despite similar objective physiological findings. Furthermore, NMO patients reported lower QOL and were at higher risk of suicide, fatigue, and hopelessness than the normal range. Nonetheless, psychiatric disturbances may receive less attention in patients with NMO because they are less likely to verbalize their distress and, as a consequence, may not receive sufficient psychiatric treatment.[9] A high level of depression is associated with poor treatment adherence,[51] low QOL, and low socioeconomic status[52] in patients with MS and NMO. Thus, treatment of psychiatric disturbances may improve quality of life and adherence to treatment. Therefore, careful screening using subjective and objective measurement tools and interventions to treat psychiatric disorders in high-risk groups are necessary for the comprehensive treatment of MS and NMO. Pharmacological treatment may be effective for an acute distress state including diagnosis and relapse. Because MS and NMO are chronic diseases, psychotherapeutic approaches including cognitive behavioral therapy and mindfulness-based cognitive therapy designed for MS and NMO patients together with a stress management program, such as biofeedback, may have long-lasting effects.

Our study has several limitations. First, our sample size was small and the participants were recruited from a single outpatient clinic. Furthermore, although the female-predominance of MS is greater in Asian countries than in Western countries,[53] the proportion of female MS participants in our study (70.8%) was higher than a previous estimate of a 1.26 female-to-male ratio of MS in Korea.[3] Moreover, our study may have had an unintentional selection bias as the mean EDSS scores were relatively low in both groups. Although our study was the largest to compare MS and NMO in Korean patients, further studies with larger sample sizes are needed to increase generalizability. Second, the cross-sectional design without a control group limited the comparability of our findings. Third, we did not adjust for potential confounding variables including previous history of mood episodes, medications including psychotropic drugs and immunosuppressants (i.e., interferon beta and corticosteroids), and relapse type. Although a recent review found that interferon beta was not clearly associated with depression,[54] several therapeutic agents with psychiatric side effects, such as corticosteroids[55] may increase the prevalence of psychiatric disturbances. Fourth, although we classified CNS lesions according to gross anatomical structures frequently involved in patients with MS and NMO, detailed description of involvements of eloquent areas for psychiatric disturbances including prefrontal area and limbic system[56] was lacking. Finally, ethnic characteristics should be considered. Asian MS patients have greater disability, more frequent involvement of the optic nerve and spinal cord, and are older at disease onset than Western patients with MS.[57] The clinical presentation of NMO overlaps with that of optic-spinal MS in Asian patients and Asian patients have a relatively high prevalence of MS compared with that in Western countries.[58] Moreover, the large number of Korean patients with relapsing-remitting MS who require frequent hospitalization[53] and the cultural tendency of Koreans to suppress negative emotion[59] may have affected the self-report questionnaire results. Although we used SCL-95, which was validated in Korean population, other questionnaires for screening psychiatric symptoms may extend reproducibility of our findings in Asian patients. By employing instruments such as Symptom Checklist-90-Revised[60] and Brief Symptom Inventory,[61] which were validated in various countries and ethnic groups and applied for screening psychiatric symptoms of various medical diseases,[62] our findings can be reproduced in further studies involving multicenter design to find psychiatric characteristics of MS and NMO patients.

In conclusion, we found that patients with MS reported higher levels of subjective depression, anxiety, panic attacks, obsessive–compulsiveness, aggression, addiction, paranoia, interpersonal sensitivity, self-regulation problems, and stress vulnerability and lower psychological QOL than did those with NMO. In contrast, we found no significant differences in the objective measures of psychiatric disturbances (i.e., PO and NB and HRV) between groups. However, QOL was lower and the levels of suicidal risk, fatigue, and hopelessness were above normal levels in patients with NMO. Disease duration was associated with various psychiatric symptoms including depression, anxiety, and suicidality in patients with MS, whereas disease duration was correlated with hopelessness, agoraphobia and somatization patients with NMO patients.

Our findings highlight the need for the screening and active treatment of psychiatric disorders in patients with MS and NMO. Future studies should focus on the implementation of tools to improve QOL and treatment outcomes in patients with MS and NMO.

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