scientific reports

OPEN

Cognitive performance in patients with neuromyelitis optica: clinical and imaging characteristics

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This study aimed to identify the prevalence, clinical and radiographic characteristics, and risk factors for cognitive dysfunction in patients with Neuromyelitis optica spectrum disorder (NMOSD). Eighty-three participants who were diagnosed with NMOSD were recruited. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) and Frontal Assessment Battery (FAB). The mean age of the patients was 47.78 ± 13.14 years, with an average of 12.05 ± 4.62 years of formal education. The majority (54%) exhibited cognitive impairment, defined by a MoCA score < 25 (mean: 22.96 ± 3.82). Disease severity (evaluated by the Expanded Disability Status Scale) and lower formal education levels were associated with cognitive impairment ($p = 0.011$ and < 0.001, respectively). The annualized relapse rate, disease duration, and AQP4 antibody status were not associated with cognitive impairment. Interestingly, informant-reported cognitive decline was associated with poorer cognitive performance ($p = 0.027$). Radiographic findings of lesion location and severity were associated with MoCA-assessed cognitive performance, particularly for lesions in the right parietal lobes ($p = 0.023$). Hippocampal atrophy was negatively correlated with FAB scores. In conclusion, approximately half of the Thai patients with NMOSD exhibited cognitive impairment, which was associated with age, formal education level, disease severity, relative perception, and specific radiological findings. Further studies incorporating comprehensive neuropsychological tests and subjective cognitive complaints are warranted.

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune demyelinating disease that leads to inflammation and destruction of white matter in the central nervous system[1]. NMOSD affects all age groups and predominates in females[2,3]. In Thailand, the disease is more prevalent than multiple sclerosis, another autoimmune demyelinating disease, resulting in greater morbidity and impaired quality of life[2,4].

According to studies[3,5–11], the reported prevalence of cognitive decline in patients with NMOSD is 30–70%, a range that varies with the study methodology and cognitive assessment tests employed. The primary deficits are slowed information processing, episodic memory decline, executive function impairment, and attention deficits[3,6,7,9,12,13]. Higher educational levels are protective against cognitive decline[3,9,10]. Physical factors have demonstrated both correlations and noncorrelations with cognitive levels[3,8–10,13,14]. Older adults tend to exhibit greater attention and verbal memory impairments than younger individuals[3,8,15]. Furthermore, radiological characteristics observed in brain magnetic resonance imaging (MRI) correlate with the degree and types of cognitive decline in patients with NMOSD[3,7].

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Various assessments have been used to evaluate cognitive function in patients with NMOSD. However, in resource-constrained settings, more accessible and less comprehensive tools are prioritized. The Montreal Cognitive Assessment (MoCA) is widely used for quickly assessing global cognitive function[16]. Studies have shown significantly lower MoCA scores in patients with NMOSD than in healthy controls[6,17]. The validated Thai version of the MoCA uses a cutoff score of less than 25 to indicate cognitive impairment[18]. The Frontal Assessment Battery (FAB), consisting of six subtests, is a simple tool for assessing frontal lobe dysfunction and can be administered by any practitioner[19]. No studies have yet evaluated FAB in patients with NMOSD.

This research aimed to study the prevalence and characteristics of cognitive impairment in patients with NMOSD at Siriraj Hospital using accessible tools, including the MoCA and FAB, and their correlation with radiological features. Additionally, we examined factors related to cognitive impairment, such as baseline patient characteristics, subjective cognitive complaints from patients and informants, and other NMOSD-related factors.

Methods

Participants
This cross-sectional study received approval from the Institutional Review Board, Faculty of Medicine Siriraj Hospital (Si 576/2019), in full compliance with international guidelines for human research protection, including the Declaration of Helsinki and the International Conference on Harmonization in Good Clinical Practice. Written informed consent was obtained from each participant. Eligible participants were recruited from Siriraj Hospital between August 2019 and August 2020. The inclusion criterion for patients was a diagnosis of NMOSD according to the 2015 International Panel for Neuromyelitis Optica Diagnosis criteria[1], with the last attack occurring more than 3 months before enrollment. Patients were excluded if they did not voluntarily participate, had a dementia diagnosis from other causes, had any active primary psychiatric disorder other than depression, or had physical limitations for cognitive testing based on the Expanded Disability Status Scale (EDSS).

Demographic data and laboratory assessment
We collected primary demographic data and clinical information from participants and informants: age, sex, handedness, formal education level, occupation, comorbidities, and subjective cognitive complaints (such as episodic memory loss or slow thought-processing speed). Regarding the clinical characteristics of patients with NMOSD, we recorded age at onset, disease duration, presentation of each attack, aquaporin-4 (AQP4) antibody status, which was determined by cell-based assay, number of relapses, and previous and current medications. The EDSS scores were obtained[20]. Brain MRIs from each participant were evaluated for T2 lesions, their locations, and gadolinium-enhanced lesions.

Cognitive assessment
Eligible participants and their informants were questioned about any perceived cognitive decline in the former. All participants underwent cognitive assessment using the Thai version of the MoCA[18] and the FAB[19]. One investigator determined the scores for all seven MoCA subcategories (Visuospatial/Executive, Naming, Attention, Language, Abstraction, Delayed Recall, and Orientation), the total MoCA score, and the time required to complete the test. In the letter fluency task of the MoCA Language subcategory and in the Lexical Fluency subcategory of the FAB, the number of words starting with the Thai letters "Koh" and "Soh," respectively, was recorded. The Memory Index Score[21], which is derived from the Delayed Recall subtest in the MoCA, was calculated (score range: 0–15). A MoCA cutoff score of less than 25 was used to define the cognitively impaired group[16,22].

MRI characteristics
The MRI Brain scans at remission of eligible participants were reviewed. The deep white matter lesions were assessed using the Fazekas scale[23]. The Fazekas scale assigns scores of 1 for punctate lesions, 2 for mild confluence lesions, and 3 for large confluence lesions. The Fazekas scale was also applied to evaluate white matter lesions in each lobe of the brain. The degree of medial temporal lobe atrophy was evaluated using the medial temporal lobe atrophy scale[24,25], which employs scores ranging from 0 to 4. This assessment evaluates the choroidal fissure width, temporal horn, and hippocampal formation height on a five-point scale (0–4). Higher scores indicate greater hippocampal atrophy. Additionally, global brain shrinkage was assessed using the global cortical atrophy scale, with scores ranging from 0 (no atrophy) to 3 (severe atrophy)[26].

Statistical analysis
Data analyses were performed using Stata Statistical Software, release 18 (StataCorp LLC, College Station, TX, USA). The data distribution was tested using the Kolmogorov–Smirnov test and Levene's test for equality of variances. Baseline characteristics and clinical data were analyzed using descriptive statistics. The results are presented as frequencies, percentages, means with standard deviations (SDs), or medians with interquartile ranges (IQRs). Comparisons between patients with cognitive impairment (MoCA score < 25) and those with preserved cognition (MoCA score ≥ 25) were analyzed using unpaired t-tests, chi-square tests, or Fisher's exact tests. A subsequent partial correlation analysis was conducted for participant characteristics, accounting for age, sex and years of formal education. Correlations between continuous data on clinical and radiological characteristics and cognitive test scores, including each subsection, are presented using Spearman's correlation coefficients. A p value less than 0.05 indicated statistical significance.

Results

Demographic data

Eighty-three patients with NMOSD participated in this study (Table 1). The cohort was predominantly female (82.9%), with a mean age of 47.8 ± 13.1 years and an average formal education level of 12.1 ± 4.6 years. During the study, 75.9% of patients were employed. Fifty-five participants (66.3%) complained of memory decline, and 47 (56.6%) reported slow brain-processing speed. Informant complaints about cognitive problems, primarily from relatives, were noted in 25 participants (30.1%). Only six participants (7.2%) had a diagnosis of depression.

Clinical characteristics of Patients with NMOSD

Serum AQP4 IgG was detected in 74 (89.2%) participants. The average age at onset was 38.4 ± 13.5 years, with a mean disease duration of 9.2 ± 7.2 years. The median annualized relapse rate was 0.44 (IQR 0.27–0.83). The

Demographic data (*n* = 83)	
Female, *n* (%)	76 (91.57%)
Age, y (mean ± SD)	47.78 ± 13.14
Education, y (mean ± SD)	12.05 ± 4.62
Presence of AQP-4-IgG, *n* (%)	74 (89.16%)
Subjective cognitive complaint, *n* (%)	
Memory *n* (%)	28 (33.73%)
Slow thought-processing speed, *n* (%)	36 (43.37%)
Cognitive tests	**Scores (mean ± SD)**
MoCA score, adjusted with education (30)	22.96 ± 3.82
Visuospatial/Executive (5)	3.84 ± 1.32
Naming (3)	2.88 ± 0.45
Attention (6)	4.92 ± 1.16
Language (3)	1.81 ± 0.93
Abstraction (2)	1.46 ± 0.72
Delayed Recall (5) *	2.00 (1.00–3.00)
Orientation (6)	5.90 ± 0.37
FAB score (18)	15.27 ± 2.47
Similarities (3)	2.17 ± 0.86
Lexical Fluency (3)	2.08 ± 1.01
Motor Series (3)	2.90 ± 0.40
Conflicting Instructions (3)	2.71 ± 0.67
Go No-Go (3)	2.49 ± 0.74
Prehensive Behavior (3)	2.95 ± 0.26
Other scores	
Memory Index Score (15)	8.89 ± 3.65
Lexical Fluency "Koh" †, number of words	8.93 ± 4.40
Lexical Fluency "Soh" †, number of words	8.36 ± 4.37
Neuroimaging findings (n = 76)	**n (%)**
Lesions compatible with NMOSD	61 (80.2)
Optic nerve lesion	14 (18.4)
Area postrema	14 (18.4)
Cerebral lesion	8 (10.5)
Brainstem lesion	28 (36.8)
Diencephalic lesion	0 (0)
Spinal cord	20 (26.32)
Subcortical white matter lesion	
Right frontal lobe lesion	47 (61.8)
Left frontal lobe lesion	49 (64.5)
Right parietal lobe lesion	30 (39.5)
Left parietal lobe lesion	28 (36.8)
Others‡	9 (11.8)

Table 1. Summary of participants' characteristics, cognitive assessments, and radiological findings. *FAB* Frontal Assessment Battery, *MoCA* Montreal Cognitive Assessment, *NMOSD* neuromyelitis optica spectrum disorder, *SD* standard deviation *Data are presented as medians with interquartile ranges. †Thai letters "ก" and "ส." ‡This includes the left and right temporal lobes and the occipital lobes.

most common presentations were myelitis (68.7%) and optic neuritis (62.7%). The median duration since the last relapse was 42 months (IQR 15–74).

NMOSD severity, according to the EDSS score, was mild (EDSS < 3) in approximately half of the participants (54%). Residual cerebral lesion symptoms, such as decreased mental acuity or fatigue, were detected in only 1.2% of patients during the remission period. Participants used various medications that may affect cognition, including gamma-aminobutyric acid modulating agents (46, 55.4%), anticholinergic drugs (60, 72.3%), and muscle relaxants (71, 85.5%). Vitamin D levels were within the standard limits in almost all patients; most patients received vitamin D supplements regardless of their levels.

Cognitive assessment results
The mean MoCA score was 22.96 ± 3.82, and the mean time to complete the MoCA was 10.4 ± 2.57 min. On average, Patients with NMOSD could recall only 1.96 items in the 5-item Delayed Recall subcategory. The mean Memory Index Score derived from the MoCA was 8.9 ± 3.7 out of 15, indicating moderate improvement of recall memory with a cue.

The mean FAB score was 15.27 ± 2.47, suggesting only mild frontal lobe dysfunction in the patients with NMOSD. The two affected subcategories were Lexical Fluency and Similarities.

Table 1 presents the details of the patient characteristics and cognitive test results.

Correlation between subjective cognitive complaints and cognitive assessments
The groups that had informant complaints had lower adjusted MoCA scores (mean = 21.56, SD = 0.81) than those without complaints (mean = 23.57, SD = 0.47; $t[81] = -2.25$, $p = 0.03$). Analysis of individual MoCA components revealed that informant complaints were associated with decreased scores for the Delayed Recall ($t[81] = -2.61$, $p = 0.01$) and Orientation ($t[81] = -2.39$, $p = 0.02$) subcategories, as well as with a lower Memory Index Score ($t[81] = -2.52$, $p = 0.01$). No correlation was found between participant or informant complaints and FAB scores. Supplementary Table S1 includes additional analyses between complaints and cognitive assessments.

Radiological characteristics of participants
Complete brain or spinal cord MRI data were available for 76 participants, with a median duration of 15 months before study enrollment. T2 hyperintense lesions were present in 93.9% of participants, and 92.2% of those lesions were compatible with an NMOSD diagnosis. Most T2 lesions were located in the spinal cord (65.9%), cerebral hemisphere (61.4%), and optic nerve (48.8%). Lesions associated with cognitive pathways were found in the caudate (3, 3.95%), globus pallidus (8, 10.53%), and thalamus (13, 17.11%). Gadolinium-enhanced lesions were observed in 24.7% of the participants.

Correlations between radiological findings and cognitive assessments
The MoCA score ($r = -0.285$, $p = 0.023$) and the Delayed Recall subscore of the MoCA ($r = -0.268$, $p = 0.033$) were negatively correlated with subcortical white matter lesions in the right parietal lobe. The Memory Index Score was also associated with right parietal lobe lesions ($r = -0.313$, $p = 0.012$). The letter fluency for the Thai letter "Koh" in the MoCA was associated with lesions in both parietal lobes (left: $r = -0.356$, $p = 0.004$; right: $r = -0.285$, $p = 0.020$). In contrast, the letter fluency for the Thai letter "Soh" in the FAB was not associated with any lesion. The time to complete the MoCA was positively correlated with lesions in the left frontal lobe ($r = 0.289$, $p = 0.021$) and both parietal lobes (left: $r = 0.362$, $p = 0.004$; right: $r = 0.406$, $p = 0.001$). However, the FAB scores did not correlate with subcortical white matter lesions.

Left hippocampal atrophy was associated with the time to complete the MoCA ($r = 0.322$, $p = 0.018$). Both left and right hippocampal atrophy were significantly associated with the total FAB score (left: $r = -0.288$, $p = 0.038$; right: $r = -0.363$, $p = 0.007$) and the Go No-Go subscore of the FAB (left: $r = -0.312$, $p = 0.025$; right: $r = -0.393$, $p = 0.050$). Left hippocampal atrophy was also associated with the FAB Similarity subscore ($r = -0.327$, $p = 0.016$).

Global cortical atrophy was positively correlated with the time to complete the MoCA ($r = 0.328$, $p = 0.018$). Cerebral microbleeds were associated with the Visuospatial/Executive subscore of the MoCA ($r = -0.284$, $p = 0.044$) and the Similarities subscore of the FAB ($r = -0.355$, $p = 0.008$). No discernible connection was found between cognitive performance and periventricular lesions.

Table 2 presents the correlations between the radiographic findings and the cognitive test results.

Comparison between participants with or without cognitive impairments
Patients with cognitive impairment had significantly lower formal education levels than those with preserved cognition (9.9 vs 14.6 years, $p < 0.001$). No significant differences were found between participants with impaired cognition (MoCA < 25) or preserved cognition (MoCA ≥ 25) in age, sex, vascular comorbidities, subjective cognitive complaints in either the memory or nonmemory domain, AQP4 antibody status, age at NMOSD onset, or disease duration (all $p > 0.05$).

There was no significant difference in disease severity between patients with cognitive impairment and those with preserved cognition ($p = 0.093$). However, when stratifying patients with NMOSD based on EDSS into mild, moderate, and severe groups, there were significant differences in severity between groups of patients with cognitive impairment and preserved cognitive ($p = 0.011$). Table 3 presents detailed comparisons between participants with and without cognitive impairment.

Items	Fazeka's scale r (p)	Subcortical white matter lesion						Hippocampal atrophy r (p)		Global cortical atrophy r (p)	Cerebral microbleed r (p)
		Frontal lobe r (p)		Temporal lobe r (p)		Parietal lobe r (p)					
		Right	Left	Right	Left	Right	Left	Right	Left		
Montreal cognitive assessment (MoCA)											
MoCA (total score)	0.105 (0.407)	−0.026 (0.841)	−0.243 (0.053)	0.200 (0.115)	0.097 (0.456)	−0.285 * (0.023)	−0.287 (0.060)	−0.134 (0.350)	−0.216 (0.125)	0.007 (0.959)	−0.209 (0.139)
Visuospatial/Executive	0.029 (0.822)	−0.030 (0.814)	−0.158 (0.212)	0.173 (0.170)	0.020 (0.892)	−0.227 (0.072)	−0.212 (0.093)	−0.054 (0.699)	−0.087 (0.544)	0.026 (0.860)	−0.284 * (0.044)
Naming	−0.056 (0.659)	−0.135 (0.295)	−0.225 (0.051)	0.094 (0.581)	−0.112 (0.369)	−0.163 (0.210)	−0.185 (0.093)	−0.089 (0.481)	−0.118 (0.390)	−0.079 (0.557)	−0.127 (0.361)
Attention	0.049 (0.700)	−0.003 (0.985)	−0.194 (0.123)	0.158 (0.214)	0.083 (0.530)	−0.234 (0.063)	−0.155 (0.222)	−0.055 (0.694)	0.111 (0.439)	0.144 (0.309)	−0.218 (0.127)
Language	0.080 (0.531)	0.021 (0.869)	−0.133 (0.295)	0.142 (0.271)	0.036 (0.781)	−0.174 (0.168)	−0.226 (0.072)	0.164 (0.249)	0.103 (0.476)	−0.032 (0.824)	−0.002 (0.988)
Abstraction	0.102 (0.422)	0.069 (0.584)	−0.031 (0.818)	0.111 (0.404)	−0.033 (0.763)	0.011 (0.935)	0.044 (0.735)	−0.142 (0.322)	−0.208 (0.155)	0.0798 (0.580)	0.059 (0.721)
Delayed Recall	−0.018 (0.890)	−0.179 (0.158)	−0.225 (0.074)	0.066 (0.610)	−0.029 (0.823)	−0.268 * (0.033)	−0.203 (0.108)	−0.241 (0.085)	−0.218 (0.121)	−0.193 (0.171)	−0.102 (0.482)
Orientation	0.023 (0.863)	−0.100 (0.459)	−0.074 (0.606)	−0.013 (0.332)	−0.142 (0.294)	−0.217 (0.093)	−0.239 (0.067)	−0.071 (0.542)	0.098 (0.445)	−0.085 (0.533)	0.094 (0.691)
Memory Index Score	0.008 (0.948)	−0.058 (0.648)	−0.234 (0.063)	−0.016 (0.903)	0.008 (0.952)	−0.313 * (0.012)	−0.161 (0.202)	−0.246 (0.079)	−0.205 (0.147)	−0.161 (0.253)	−0.049 (0.735)
Time to complete MoCA	0.073 (0.568)	0.216 (0.087)	0.289 * (0.021)	0.008 (0.952)	−0.060 (0.645)	0.406 * (0.001)	0.362 * (0.004)	0.217 (0.123)	0.322 * (0.018)	0.328 * (0.018)	−0.198 (0.163)
Frontal assessment battery (FAB)											
FAB (Total score)	−0.020 (0.873)	−0.076 (0.552)	−0.213 (0.092)	0.079 (0.546)	0.143 (0.789)	−0.169 (0.181)	−0.157 (0.215)	−0.288 * (0.038)	−0.363 * (0.007)	−0.133 (0.345)	−0.239 (0.089)
Similarities	0.102 (0.422)	−0.062 (0.626)	−0.060 (0.638)	0.138 (0.285)	0.064 (0.629)	−0.163 (0.198)	−0.144 (0.256)	−0.146 (0.304)	−0.327 * (0.016)	0.069 (0.625)	−0.355 * (0.008)
Lexical Fluency	−0.099 (0.435)	−0.011 (0.932)	−0.225 (0.073)	−0.048 (0.706)	0.020 (0.888)	−0.186 (0.141)	−0.225 (0.075)	−0.046 (0.744)	−0.100 (0.487)	−0.076 (0.588)	0.005 (0.986)
Motor Series	−0.013 (0.916)	0.054 (0.670)	0.077 (0.544)	0.062 (0.621)	0.062 (0.621)	−0.032 (0.797)	−0.046 (0.712)	−0.071 (0.568)	−0.092 (0.473)	−0.128 (0.371)	−0.156 (0.269)
Conflicting Instructions	−0.032 (0.802)	0.022 (0.854)	−0.06 (0.977)	0.002 (0.941)	−0.002 (0.801)	−0.224 (0.078)	−0.185 (0.147)	−0.039 (0.740)	0.107 (0.480)	−0.039 (0.763)	−0.224 (0.141)
Go No-Go	−0.094 (0.457)	−0.173 (0.168)	−0.225 (0.070)	0.114 (0.388)	0.074 (0.600)	−0.192 (0.130)	−0.126 (0.322)	−0.312 * (0.025)	−0.393 * (0.050)	−0.261 (0.065)	−0.254 (0.083)
Prehensive Behaviour	0.013 (0.921)	−0.172 (0.164)	−0.155 (0.215)	0.065 (0.993)	0.065 (0.993)	0.042 (0.789)	0.028 (0.879)	−0.199 (0.231)	−0.232 (0.190)	−0.043 (0.703)	0.071 (0.978)
Other scores											
Letter Fluency: "Koh" †	−0.040 (0.753)	−0.199 (0.115)	−0.156 (0.217)	−0.006 (0.962)	−0.063 (0.627)	−0.285 * (0.020)	−0.356 * (0.004)	−0.029 (0.839)	−0.155 (0.279)	−0.255 (0.068)	−0.210 (0.138)
Letter Fluency: "Sor"†	−0.074 (0.562)	0.026 (0.984)	−0.224 (0.075)	0.008 (0.952)	0.066 (0.609)	−0.116 (0.360)	−0.167 (0.186)	−0.162 (0.254)	−0.197 (0.164)	−0.125 (0.377)	−0.039 (0.789)

Table 2. Correlations between cognitive assessments and radiological findings. *AQP4* aquaporin-4, *EDSS* expanded disability severity scale, *FAB* Frontal Assessment Battery, *MoCA* Montreal Cognitive Assessment. *Statistically significant ($p < 0.05$). †Thai letters "ก" and "ส."

Factors associated with cognitive performance

The study revealed significant associations between several cognitive measures (MoCA score, Memory Index Score, time to complete the MoCA, and FAB score) and various demographic and clinical factors. These factors were age, formal-educational level, age at onset, and EDSS score (disease severity). All associations were significant at $p < 0.05$ (Fig. 1 and Table 4). However, no significant correlations were observed after adjusting for age, sex, and years of formal education ($p > 0.05$) (Supplementary Table S2).

Discussion

In our study, 54% of the Thai patients with NMOSD at Siriraj Hospital experienced cognitive impairment, according to the MoCA. The mean MoCA score was 22.96, which is below the cutoff point for the Thai population[16,18,22]. This finding is similar to that of a previous study on Asian Patients with NMOSD by Zhang et al.[8], which included the MoCA. Their investigation revealed a lower MoCA score in Patients with NMOSD than in healthy controls, with a mean score 24.42.

Previous studies on cognitive impairment in patients with NMOSD have reported a prevalence of 30–70%, which is consistent with our findings[3,5–9]. A meta-analysis reported significantly worse cognitive function in patients with NMOSD than in healthy subjects, particularly in attention, language, short-term memory, information-processing speed, and executive function[6,12]. Our results align with these findings, as indicated by the

	Participants with cognitive impairment $n = 45$	Participants with preserved cognition $n = 38$	p
Baseline demographic data			
Female, *n* (%)	40 (88.9)	37 (97.4)	0.212
Age, y	48.8 ± 14.64	46.6 ± 11.2	0.446
Years of education, y	9.9 ± 4.3	14.6 ± 3.6	< 0.001
Presence of vascular comorbidity, *n* (%)	14 (31.1)	5 (13.2)	0.052
Subjective memory complaint, *n* (%)	28 (62.2)	27 (71.1)	0.397
Subjective complaint of slow brain processing, *n* (%)	28 (62.2)	19 (50.0)	0.263
Informant report of cognitive decline, *n* (%)	16 (35.6)	9 (23.7)	0.240
Depressed mood, *n* (%)	4 (8.9)	2 (5.3)	0.683
Clinical characteristics of NMOSD			
Age at onset, years	38.3 ± 15.1	38.45 ± 11.5	0.952
Duration of disease, years *	9.0 (4.5–16.5)	6.5 (3.8–12.3)	0.088
Median EDSS score *	3.0 (1.0–5.5)	2.0 (1.0–3.5)	0.093
Severity category			
Mild: EDSS < 3, *n* (%)	20 (44.4)	25 (65.8)	
Moderate: EDSS 3–6, *n* (%)	17 (37.8)	13 (34.2)	0.011
Severe: EDSS > 6, *n* (%)	8 (17.8)	0	
Presence of AQP4 antibodies, *n* (%)	38 (84.4%)	36 (94.7%)	0.170
Number of relapses *	3.0 (2.0–6.0)	3.0 (2.0–6.0)	0.488
Annualized relapse rate for first 5 years *, † (*n* = 57)	0.6 (0.4–1.0)	0.6 (0.4–1.2)	0.320
Duration since the last relapse, mo *	44.0 (16–79.5)	31.0 (14.5–65.8)	0.583
Vitamin D level (*n* = 65)	35.3 ± 9.2	38.9 ± 13.4	0.162
Cognitive assessment			
MoCA	26.2 ± 1.4	20.2 ± 2.9	0.001
Time to finish MoCA, min (*n* = 64)	11.8 ± 2.5 (*n* = 36)	8.9 ± 1.6 (*n* = 33)	< 0.001
Frontal Assessment Battery scores	14.2 ± 2.8	16.5 ± 1	< 0.001
Other tests scores			
Memory Index Score	7.4 ± 4.0	10.6 ± 2.3	< 0.001
Lexical Fluency: "Koh" ‡	7.2 ± 3.8	11.0 ± 4.3	< 0.001
Lexical Fluency: "Soh" ‡	6.7 ± 3.7	10.4 ± 4.3	< 0.001

Table 3. Comparison of baseline demographic and clinical characteristics of neuromyelitis optica spectrum disorder participants with and without cognitive impairment defined by Montreal Cognitive Assessment score. *AQP4* aquaporin-4, *EDSS* Expanded Disability Status Scale, *FAB* Frontal Assessment Battery, *MoCA* Montreal Cognitive Assessment, *NMOSD* neuromyelitis optica spectrum disorder. *Data are presented as medians with interquartile ranges. †Included only participants who had a disease duration of more than 5 years (*n* = 57). ‡Thai letters "ก" and "ส."

MoCA subscores in each domain. The cognitive tests in our study were not specifically designed to evaluate information processing speed. Consequently, we endeavored to gauge impairments in brain processing speed via the MoCA testing time as well as the number of words generated in MoCA's Language subtest and FAB's Lexical Fluency component.

The factors affecting cognition in the patients with NMOSD in our study were formal education level and disease severity, as defined by the EDSS score. Our comparison of EDSS scores between groups revealed significantly better scores in the cognitively preserved group. Additionally, we found significant correlations between MoCA scores and age, age at disease onset, years of formal education, disease severity according to the EDSS score, FAB score, and time to complete the MoCA. However, after adjusting for age and formal educational level, there was no significant correlation between MoCA scores and disease severity. This finding may be explained by the influence of age and years of formal education on cognitive impairment, consistent with previous studies[8,10,13,14].

An interesting finding was the significance of complaints from patients' relatives. Our study showed that the MoCA scores of patients were significantly lower when their relatives reported the patient's cognitive problems, regardless of whether the patients themselves reported cognitive issues. In contrast, when only the patients reported experiencing cognitive difficulties, without their relatives reporting any problems, the MoCA scores did not differ significantly from those of patients whose relatives did not report any cognitive concerns. No previous NMOSD study has mentioned this finding, but studies in other diseases, including Alzheimer's disease, have shown correlations between informant perception and objective cognitive decline[27–32].

Our analysis of radiological findings revealed correlations between the severity and location of brain lesions observed on MRI scans and the affected brain areas. Specifically, lesions in the right parietal lobe were linked to lower MoCA scores and subscores (particularly for Delayed Recall) as well as Memory Index Scores. This
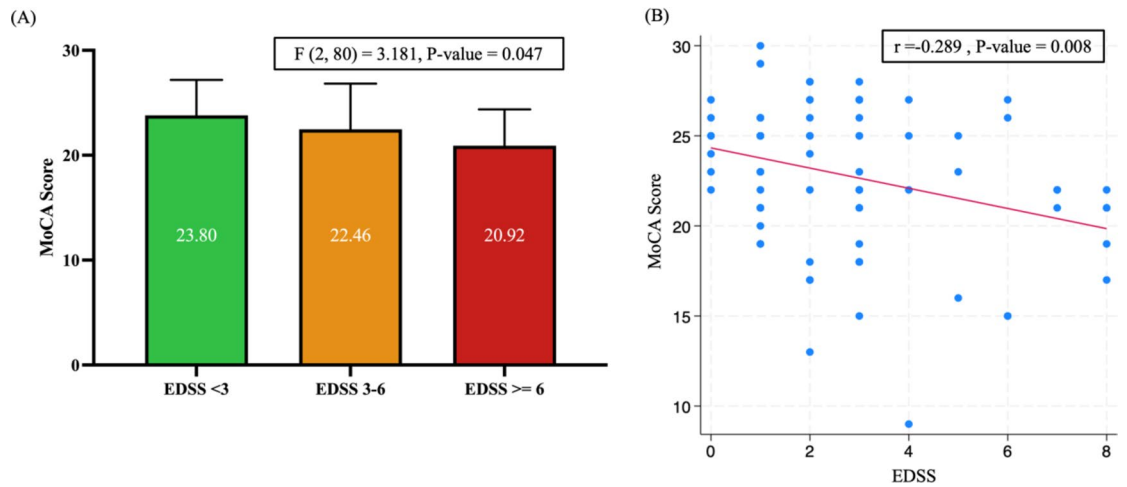
(A)

(B)

Fig. 1. Association between severity of disease and Montreal Cognitive Assessment score. Abbreviations: EDSS, Expanded Disability Status Scale; MoCA, Montreal Cognitive Assessment. (**A**) Analysis of variance between patients with mild (EDSS < 3), moderate (EDSS 3–6), and severe (EDSS ≥ 6) disease severity, demonstrating a significant difference in MoCA scores. (**B**) Scatterplot showing negative correlations between EDSS and MoCA scores.

Factors	MoCA score		Memory index score		Time to complete MoCA		FAB score	
	Correlation coefficient (r)	p	Correlation coefficient (r)	p	Correlation coefficient (r)	p	Correlation coefficient (r)	p
Age	− 0.260 *	0.017	− 0.354 *	0.010	0.344 *	0.004	− 0.359 *	0.001
Years of education	0.598 *	< 0.001	0.408 *	< 0.001	− 0.586 *	0.000	0.580 *	< 0.001
Disease duration	− 0.004	0.974	0.046	0.677	0.071	0.568	− 0.036	0.744
Age of onset	− 0.247 *	0.024	− 0.370 *	0.006	0.284 *	0.019	− 0.032 *	0.003
EDSS score	− 0.289 *	0.008	− 0.237 *	0.031	0.191	0.120	− 0.277 *	0.039
Number of relapses	0.109	0.327	0.063	0.570	− 0.054	0.965	0.005	0.966
Vitamin D level	0.077	0.493	0.101	0.370	− 0.119	0.343	− 0.074	0.509

Table 4. Factors correlated with cognitive performance. *EDSS* Expanded Disability Status Scale, *FAB* Frontal Assessment Battery, *MoCA* Montreal Cognitive Assessment. *Statistically significant ($p < 0.05$).

finding was likely due to the association of the parietal cortex with episodic memory[33,34]. Similarly, the association between impairment in letter fluency for the Thai letter "Koh" and bilateral parietal lobe lesions aligns with previous research showing parietal lobe activation during letter fluency tasks in PET scans[35–37]. Interestingly, we noted that lesions in the left frontal and left parietal lobes were associated with the time to complete the MoCA but not with the MoCA score. This finding suggests that such lesions have a subtle effect on brain processing speed that is not directly reflected in the MoCA score.

Consistent with previous studies, FAB and subtests, such as the Go No-Go test, were negatively associated with medial cortical atrophy and hippocampal atrophy[38]. Our study showed that while global cortical atrophy is not associated with MoCA scores, it is associated with the time to complete the MoCA, indicating slower brain processing speed. Furthermore, we observed associations between cortical microbleeds and visuospatial function, as reflected in the MoCA subscores, similar to previous reports in patients with Alzheimer's disease[39].

It is worth mentioning that this study enrolled a large number of patients with NMOSD and was the first to explore cognition among patients with NMOSD in Thailand. We utilized the accessible MoCA and FAB, which can be easily applied in clinical practice. This study also included the assessment of subjective cognitive complaints reported by patients (self-reports) and their relatives (informant reports). This approach has not been previously utilized for patients with NMOSD.

There are several limitations to this study. First, we used only the MoCA and the FAB to assess cognitive function, which might not fully represent all affected cognitive domains. More studies using comprehensive neuropsychological tests are required to describe the characteristics of cognitive problems in patients with NMOSD. However, the tests we used (MoCA and FAB) are accessible and applicable to outpatient settings with limited time and resources. Second, the time to complete the MoCA may vary based on the speech speed of different examiners. To minimize this issue, we used only one examiner for the instructions. Third, only a small number of participants reported a depressed mood. Depression is a well-described factor associated with cognitive decline and has a high prevalence in patients with NMOSD, reaching 42.8–58.3%[5,10,11]. The surprisingly low prevalence of depression in this study might be because the screening assessment we used for depression was

only the self-reported Patient Health Questionnaire-2[40]. More assessments of mood problems are needed, and the correlation between depression and cognitive problems should be examined further.

Conclusions

Most of the Thai patients with NMOSD had cognitive impairment, which was associated with formal education level, disease severity, and the perceptions of their relatives. Correlations were found between cognition and NMOSD radiographic characteristics. Further studies using more comprehensive cognitive tests, including evaluations of mood, behavior, and subjective cognitive complaints, are needed for better future care of patients with NMOSD.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Acknowledgements

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Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-71176-x.

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