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Can the Age of the First Symptom of Neuromyelitis Optica be Used to Predict Cognitive Impairment?

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Abstract

Objective: Cognitive functions, including working memory, attention, word fluency, and information processing speed, are known to be impaired in persons with multiple sclerosis (pwMS). Despite the clinical similarity of cognitive symptoms between persons with neuromyelitis optica (pwNMO) and pwMS, there is a dearth of research addressing cognitive impairment (CI) in NMO-related literature. This study aimed to examine the potential link between the age of initial symptom onset (ISO) and the presence of CI in pwNMO.

Materials and Methods: This study comprised two groups of pwNMO: eleven patients with age at ISO between 18 and 29, and 15 with age at ISO between 30 and 50. To mitigate the confounding effects on CI, pwNMO with matched education levels and ages were included in the study. A cohort of 467 healthy controls was assessed using the Brief International Cognitive Assessment for Multiple Sclerosis battery with a predefined cut-off value for CI set at 1.5 standard deviations below the mean. Participants with scores below this threshold value were classified as exhibiting CI in the respective domains. The severity of CI was stratified based on the number of impacted domains: participants exhibiting impairment in one domain were classified as experiencing moderate-to-severe impairment, those with impairment in two domains as severe, and those with impairment across all three domains as very severe.

Results: None of the pwNMO who developed ISO between the ages of 18-29 exhibited CI. However, among those with ISO between the ages of 30 and 50, three demonstrated moderate-to-severe CI, one experienced severe CI, and one showed very severe CI.

Conclusion: The study results indicate a potential link between the age at ISO and the development of CI in pwNMO. Specifically, none of the pwNMO who experienced ISO between the ages of 18 and 29 exhibited signs of CI, whereas a significant percentage of those who experienced ISO between the ages of 30 and 50 showed signs of CI to varying degrees. These findings indicated that the onset of NMO symptoms at a later age may raise the risk of developing CI. Therefore, an early initiation of treatment could be vital in preventing and managing CI in pwNMO. Additional research is warranted to validate these findings and clarify the underlying mechanisms causing this connection.

Keywords: NMOSD, cognitive impairment, age, first symptom

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune, inflammatory disease of the central nervous system affecting the optic nerve and spinal cord (1). The prevalence of NMOSD ranges from 0.07 to 10 per 100,000, while its incidence varies from 0.029 to 0.880 per 100,000. Compared to other demyelinating illnesses, it is less frequently observed

(2). Although the disease mainly affects the optic nerve and spinal cord, it may also involve the brain parenchyma, third ventricle, and periaqueductal areas (3,4). Autoantibodies against astrocytes have been identified in most NMOSD patients (5). Two different definitions of seropositive and seronegative NMOSD are employed based on the presence of antibodies against the aquaporin four channels (6,7). These

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autoantibodies are present throughout the central nervous system, particularly in the optic nerves and spinal cord (8). They are especially evident in the periventricular regions (9). Despite the widespread belief that the cerebrum is preserved in NMO, recent research has revealed that 60% of NMO patients develop cerebral lesions (8,10). While the relationship between multiple sclerosis (MS) and cognitive functions has been well established and demonstrated in numerous studies, research on the effects of NMO on cognitive functions appears to be significantly scarce. According to recent research, NMO patients have a 30% to 70% prevalence of cognitive impairment (Cl) (11). Studies involving patients with NMO and MS have demonstrated that both groups have similar cognitive profiles and that there are alterations in attention, memory, information processing speed, and verbal fluency (12-15). There is no standardized test for assessing cognitive functions in NMOSD patients. Most studies employed batteries applied for evaluating cognitive function in MS patients (9,12-21). Not every cognitive domain was assessed in these studies. Although visual and verbal memory, attention, verbal fluency, and executive functions were measured in most studies (11,14,16-20), some studies assessed only a single domain, such as attention or executive functions, to evaluate cognition (21,22). Studies on NMO have focused on serological variables, education level, depression and anxiety, brain atrophy, and lesions in gray and white matter (11-15,17,19-21). Cognitive functions such as working memory, attention, word fluency and information processing speed have been shown to be impaired in MS patients. Few studies in the NMO literature have addressed CI, despite the clinical similarities in cognitive symptoms between patients with neuromyelitis optica and MS. Due to a paucity of studies examining the effect of age at first symptom on cognition in NMO patients, we focused on this aspect across all cognitive domains.

Materials and Methods

Participants

This retrospective study included twenty-six persons with NMO (PwNMO) and 467 healthy controls (HCs). The HCs were selected from the relatives of patients presenting to our clinic and comprised individuals without a diagnosis of MS or NMO.

Conversely, in the 26 NMO patients, the inclusion criteria required them to have a definite diagnosis of NMOSD between the ages of 18-50 years and to have completed the Brief International Cognitive Assessment for MS (BICAMS) battery. The exclusion criteria included having experienced an attack in the previous three months, having other neurological diseases, and being unable to follow the instructions for BICAMS. Individuals with NMO were categorized according to the age at the first symptom. Two groups were formed: 11 NMOs with first symptoms appearing between 18 and 29 years of age and 15 NMOs who experienced their first symptoms between 30 and 50 years of age. To remove potential effects on CI, the study included PwNMOs with matched educational levels and no significant age difference between the two groups. The current study protocol, compared with previous data, was approved by the Karadeniz Technical University Faculty of Medicine Ethics Committee (approval no.: 3, date: 02.02.2015), and all participants provided written informed consent.

Assessment

The cognitive status was determined using the BICAMS battery, which includes the Symbol Digit Modalities Test to evaluate information processing speed, the California Verbal Learning Test-II to assess verbal memory and learning, and the Brief Visuospatial Memory Test Revised to examine visual memory and learning. Since CI in MS patients is observed in auditory, visual, and information processing speed, BICAMS is accepted as the gold standard for testing cognition in MS patients (23). This battery has been validated for the Turkish population.

The 467 HCs completed the BICAMS battery, and the cut-off value for CI was established as 1.5 standard deviation (SD) below (Table 1). Participants with performance scores for a cognitive domain below the cut-off value were deemed to exhibit CI in that domain. Those with impairment in one domain were assessed as experiencing moderate-to-severe CI, those with impairment in two domains were classified as having severe CI, and those with impairment in all three domains were deemed to have very severe CI.

The Brief Repeatable Battery of Neuropsychological Tests is frequently employed in studies to identify CI in NMO patients.

Table 1. Study population and criteria						
Group	Number of participants	Include criteria	Exclusion criteria			
PwNMO (18-29)	11	Definite diagnosis of NMOSD	Attack in the last three months, other neurological diseases, non- compliance with BICAMS.			
PwNMO (30-50)	15	Definite diagnosis of NMOSD	Attack inthe last three months, other neurological diseases, non- compliance with BICAMS.			
НС	467	Healthy, age 18-50, completed BICAMS	Not applicable			

PwNMO: Persons with neuromyelitis optica, HC: Healthy control, BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis, NMOSD: Neuromyelitis optica spectrum disorder

J Mult Scler Res 2025;5(1):3-7

In the available research, NMO patients with CI comparable to MS patients have not been evaluated using the BICAMS battery. In this context, to facilitate the comparison of MS and NMO patients in terms of CI, the NMO patients in this study were assessed using BICAMS.

Statistical Analysis

The data analysis was conducted using IBM SPSS statistics software for Windows (ver. 24.0: IBM Corp., Armonk, NY, USA). The normality assumption for the data was examined employing the Shapiro-Wilk test and the histograms. The gained scores (posttest-pretest) were analyzed using the independent samples t-test. Additionally, the 95% confidence intervals were examined. A p-value <0.05 was considered to be statistically significant.

Results

In this study, 11 pwNMO with initial symptom onset (ISO) aged 18-29 years and 15 pwNMO with ISO aged 30-50 years were included. In the sporadic group, 467 individuals underwent cognitive assessment. The BICAMS (24) battery was used to conduct the cognitive evaluation. The value used for diagnosing CI was determined as 1.5 SD below the mean, and individuals with scores below this threshold were classified as exhibiting CI (Table 2).

On the BICAMS assessment, no CI was detected in the 11 pwNMO who had experienced ISO at ages 18-29. Five of the 15 pwNMO who developed ISO between the ages of 30 and 50 exhibited various levels of CI. Three of these individuals experienced moderate-severe CI, one exhibited severe CI, and one had very severe CI (Table 3).

The findings demonstrated a statistically significant relationship between the age of ISO and CI (p<0.05). Notably, no CI was detected in pwNMO with ISO in the 18-29 age group, whereas significant CI was observed in pwNMO with ISO at ages 30-50 years (Table 4).

Discussion

According to the literature, between 30% and 70% of NMOSD patients experience CI (11). Patients may exhibit deficits, especially in attention, language, memory, and information processing. A meta-analysis reported that NMOSD patients demonstrated significantly more impaired cognitive functions

Table 2. Cut-off values for classifying cognitive impairment using the BICAMS* battery				
Symbol Digit Modalities Test (SDMT)	25.2			
California Verbal Learning Test-II (CVLT-II)	34.26			
Brief Visuospatial Memory Test Revised (BVMT-R)	17.04			

*BICAMS data from 467 healthy controls below 1.5 standard deviation (SD), BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis than healthy individuals, especially in the areas of attention, language, short-term memory, information processing speed, and executive functions (25). Cognitive function in these several domains may exhibit age-related variations, with varying consequences for different age groups. Studies have revealed that older adults with NMOSD experienced more significant impairments in attention and verbal memory compared to younger individuals (19,21). Similarly, some studies have (13) examined the prevalence of CI in NMOSD patients and reported that these impairments were related to aging and disease progression.

The age at ISO should be considered when assessing cognitive functions in NMOSD patients (18). Showed that CIs in NMOSD were linked to white matter atrophy and cortical degeneration. This indicates that the development of CI, especially in the 30-50 age group, may be influenced by the neurodegenerative processes associated with aging. This study examined in detail the potential relationship between CI and age at ISO in NMOSD patients. Our results suggested a statistically significant association between the age at ISO and the development of Cl. More specifically, although we did not detect any Cl in the cognitive tests administered to patients with ISO between 18 and 29 years of age, significant CI was documented in patients with ISO between 30 and 50 years of age. Our data suggests that NMOSD symptoms that present at an older age may impact cognitive functions. Our results imply that Cls, which are more common in older age, may be due to the increasing disease burden of NMOSD with age.

The link between NMOSD and cognitive functions has not been extensively studied, so our study is important in this regard. Specifically, the impact of age at ISO on CI demonstrates

Table 3. Cognitive impairment severity levels						
Number of domains affected	Severity classification	Cut-off threshold				
One domain	Moderate-to- severe	1.5 (SD) below mean				
Two domains	Severe	1.5 (SD) below mean				
Three domains	Very severe	1.5 (SD) below mean				

SD: Standard deviation

Table 4. Severity of cognitive impairment

Severity levels	PwNMO (18-29)	PwNMO (30-50)
Number of patients with ISO	11	15
Number with Cl	0	5
Severe CI	0	3
Moderate-severe CI	0	1
Very severe CI	0	1

ISO: Initial symptom onset, CI: Cognitive impairment, PwNMO: Persons with neuromyelitis optica

the significance of evaluating cognitive findings in NMOSD patients. In addition, the lack of standardized cognitive assessment methods in NMOSD patients is a limitation. The BICAMS battery, which is commonly used in MS patients, was used in our investigation; however, it should be noted that these tests may not be able to fully capture abnormalities specific to NMOSD (19). Nevertheless, utilizing the standardized BICAMS battery for MS in the study enhanced the comparability of the results.

However, the study also has certain limitations. Patients with NMOSD frequently experience depression, a known condition linked to cognitive decline. Depression rates in these patients have been reported to be between 42.8% and 58.3% (14,25). Gathering information regarding psychiatric comorbidities (depression, anxiety) and including neurological imaging findings in the study may contribute to the elucidation of the mechanisms underlying cognitive disorders.

More precisely, one of the shortcomings is the limited sample size; future research could improve the findings' generalizability by including more patients. This study was conducted retrospectively, and the long-term effects of ISO age on CI may be better explored in future research that takes a prospective approach.

Conclusion

This study demonstrates that there is a significant relationship between the age at ISO and the development of CI in NMOSD patients. The findings imply that an older age at ISO may exacerbate the risk of developing CI, highlighting the significance of early diagnosis and intervention. Although the study provides valuable insights into the cognitive alterations associated with NMOSD, prospective research with larger, diverse groups is required to corroborate these findings and clarify the underlying mechanisms. Furthermore, considering the other parameters that may influence the cognitive findings in this patient group, participation in the analysis will make future studies more qualitative.

Ethics

Ethics Committee Approval: Was approved by the Karadeniz Technical University Faculty of Medicine Ethics Committee (approval no.: 3, date: 02.02.2015)

Informed Consent: All participants provided written informed consent

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A., U.S., E.S.Z., Concept: G.D.U., I.K., C.C., U.S., E.S.Z., Design: G.D.U., S.A., I.K., C.C., U.S., E.S.Z., Data Collection or Processing: G.D.U., I.K., C.C., U.S., E.S.Z., Analysis or Interpretation: G.D.U., S.A., C.C., U.S., E.S.Z., Literature Search: G.D.U., S.A., I.K., C.C., U.S., E.S.Z., Writing: G.D.U., S.A., C.C., U.S., E.S.Z.

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J Mult Scler Res 2025;5(1):3-7

Unal et al. ISO as a Predictor of Cognitive Impaiment in NMO

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